DESIGN AND EVALUATION OF INTRAGASTRIC BUOYANT TABLETS OF VENLAFAXINE HYDROCHLORIDE

Dissertation submitted to

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MASTER OF PHARMACY

(PHARMACEUTICS)

Submitted By

Reg. No: 26104209

Under the guidance of

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CERTIFICATE

This is to certify that the work embodied in this thesis entitled, "**DESIGN AND EVALUATION OF INTRAGASTRIC BUOYANT TABLETS OF VENLAFAXINE HYDROCHLORIDE"** submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai, was carried out by **Mr. SANATH REDDY KURAPATI,** Department of Pharmaceutics, Nandha College of Pharmacy, Erode-52 for the partial fulfillment for the award of degree of Master of Pharmacy in Pharmaceutics under my supervision.

This work is original and has not been submitted in part or full for any other degree or diploma of this or any other university.

Place : Erode **Dr. (Mrs.) P.R. Radhika, M. Pharm., Ph.D.,**

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EVALUATION CERTIFICATE

This is to certify that the work embodied in this thesis entitled, **"DESIGN AND EVALUATION OF INTRAGASTRIC BUOYANT TABLETS OF VALNAFEXINE HYDROCHLORIDE"** submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, was carried out by Reg. No. **26104209** in the Department of Pharmaceutics, Nandha College of Pharmacy and Research institute, Erode-52 for the partial fulfillment for the award of degree of **MASTER OF PHARMACY** in Pharmaceutics under the supervision and guidance of **Dr.P.R.RADHIKA, M.Pharm,PhD.,** Professor, Department of Pharmaceutics, Nandha College of Pharmacy and Research Institute, Erode- 52.

This work is original and has not been submitted in part or full for any other degree or diploma of this or any other university.

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DECLARATION

The work presented in this thesis entitled "**DESIGN AND EVALUATION OF INTRAGASTRIC BUOYANT TABLETS OF VENLAFAXINE HYDROCHLORIDE"** was carried out by me in the Department of Pharmaceutics, Nandha College of Pharmacy, Erode-52 under the direct supervision of **Dr. (Mrs.) P.R. Radhika M.Pharm., Ph.D.,** Nandha College of Pharmacy, Erode-52.

This work is original and has not been submitted in part or full for the award of any other degree or diploma of any other University.

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LIST OF ABBREVIATIONS

BP	-	British Pharmacopoeia
ºC	-	Degree Centigrade
cc	-	Cubic centimeter
Conc.	-	Concentration
CR	-	Controlled-release
DDS	-	Drug Delivery System
FD	-	Floating duration
FLT	-	Floating Lag Time
FT-IR	-	Fourier transform Infrared
FDDS	-	Floating drug delivery system
g	-	Gram
GET	-	Gastric emptying time
GIT	-	Gastric intestinal tract
GRDDS	-	Gastro retentive drug delivery system
HCl	-	Hydrochloric acid
HPMC	-	Hydroxy propyl methyl cellulose
hr	-	Hour
ICH	-	International conference on Harmonization
IR	-	Infra red
IP	-	Indian Pharmacopeia
λ max	-	Lambda maximum
MCC	-	Microcrystalline cellulose
mg	-	Milligram

ml	-	Milliliter
mm	-	Millimeter
µg	-	Microgram
µl	-	Microliter
µg /ml	-	Microgram per milliliter
MMC	-	Migrating Myoelectric Complex
#	-	Mesh
N	-	Normality
nm	-	Nanometer
%	-	Percentage
pH	-	Hydrogen ion concentration
PhEur	-	European Pharmacopoeia
PVP	-	Poly vinyl pyrolidine
Qty	-	Quantity
RH	-	Relative humidity
RPM	-	Revolution per minute
SD	-	Standard deviation
SI	-	Swelling Index
SR	-	Sustained-release
SW	-	Swollen tablet
Tab	-	Tablet
USP NF	-	United State Pharmacopoeia National Formulary
UV	-	Ultraviolet
Vol	-	Volume

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CHAPTER I

INTRODUCTION

1. INTRODUCTION

The design of an oral controlled drug delivery system (DDS) should be primarily aimed at achieving more predictable and increased bioavailability of drugs. However, the development process is precluded by several physiological difficulties, such as an inability to restrain and localize the DDS within desired regions of the gastrointestinal (GI) tract and the highly variable nature of gastric emptying process. It can be anticipated that, depending upon the physiological state of the subject and the design of pharmaceutical formulation, the emptying process can last from a few minutes to 12 hours (hr). This variability in turn may lead to unpredictable bioavailability and times to achieve peak plasma levels, since the majority of drugs are preferentially absorbed in the upper part of the small intestine. Furthermore, the relatively brief gastric emptying time (GET) in humans, which normally averages 2–3 hr through the major absorption zone (stomach or upper part of the intestine), can result in incomplete drug release from the DDS leading to diminished efficacy of the administered dose. Thus, control of placement of a DDS in a specific region of the GI tract offers numerous advantages, especially for drugs exhibiting an absorption window in the GI tract or drugs with a stability problem. Overall, the intimate contact of the DDS with the absorbing membrane has the potential to maximize drug absorption and may also influence the rate of drug absorption. These considerations have led to the development of oral controlled-release (CR) dosage forms possessing gastric retention capabilities.[1]

Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.[2]

1.1 Basic Gastrointestinal Tract Physiology: [1]

It is well recognized that the stomach may be used as a ‘depot’ for sustained-release (SR) dosage forms, both in human and veterinary applications. The stomach is anatomically divided into three parts: fundus, body, and antrum (or pylorus). The proximal stomach, made up of the fundus and body regions, serves as a reservoir for ingested materials while the distal region

(antrum) is the major site of mixing motions, acting as a pump to accomplish gastric emptying. The process of gastric emptying occurs both during fasting and fed states; however, the pattern of motility differs markedly in the two states. In the fasted state, it is characterized by an inter-digestive series of electrical events which cycle both through the stomach and small intestine every 2–3 hr. This activity is called the inter-digestive myoelectric cycle or MMC, which is often divided into four consecutive phases.

- **Phase I** is a quiescent period lasting from 40 to 60 min with rare contractions.
- **Phase II** is a period of similar duration consisting of intermittent action potentials and contractions that gradually increase in intensity and frequency as the phase progresses.
- **Phase III** is a short period of intense, large regular contractions lasting from 4 to 6 min. It is this phase, which gives the cycle the term 'housekeeper' wave, since it serves to sweep undigested materials out of the stomach and down the small intestine. As phase III of one cycle reaches the end of the small intestine, phase III of the next cycle begins in the duodenum.
- **Phase IV** is a brief transitional phase that occurs between phase III and phase I of two consecutive cycles. In the fed state, the gastric emptying rate is slowed since the onset of MMC is delayed. In other words, feeding results in a lag time prior to the onset of gastric emptying. Overall, the relatively brief GI transit time of most drug products, which is approximately 8–12 h, impedes the formulation of a once daily dosage form for most drugs. These problems can be exacerbated by alteration in gastric emptying that occur due to factors such as age, race, sex, and disease states, as they may seriously affect the release of a drug from the DDS. It is, therefore, desirable to have a CR product that exhibits an extended GI residence and a drug release profile independent of patient related variables.

1.2 Factors Affecting Gastric Retention: [3]

- **Density** – GRT is a function of dosage form buoyancy that is dependent on the density.
- **Size** – dosage form units with a diameter of more than 7.5mm are reported to have an increased GRT compared with those having diameter of 9.9mm.

- **Shape of dosage form** – tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch are reported to have better GRT ≈ 90% to 100% retention at 24 hr compared with other shapes.
- **Fed or unfed state** – under fasting conditions, the GI motility is characterized by periods of strong motor activity or MMC that occurs every 1.5 to 2 hr. The MMC sweeps undigested material from the end if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.
- **Nature of meal** – feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.
- **Caloric content** – GRT can be increased by 4 to 10 hr with a meal that is high in proteins and fats.
- **Frequency of feed** – the GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.
- **Gender** – mean ambulatory GRT in males (3.4±0.6 hr) is less compared with their age and race matched female counterparts (4.6±1.2 hr), regardless of the weight, height and body surface).
- **Age** – Elderly people, especially those over 70, have a significantly longer GRT.
- **Posture** – GRT can vary between supine and upright ambulatory states of the patient.
- **Concomitant drug administration** – anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride.
- **Biological factors** – diabetes and Crohn's disease, etc.

1.3 Gastroretentive forms: [4, 10, 11]

1. Floating systems
2. High density systems
3. Expandable systems
4. Superporous hydrogels
5. Mucoadhesive or bioadhesive systems
6. Magnetic systems

1. Floating systems

These have a bulk density lower than the gastric content. They remain buoyant in the stomach for a prolonged period of time, with the potential for continuous release of drug. Eventually, the residual system is emptied from the stomach. Gastric emptying is much more rapid in the fasting state and floating systems rely heavily on the presence of food to retard emptying and provide sufficient liquid for effective buoyancy.

2. High density systems

Gastric contents have a density close to water (1.004 g/cm^3). When the patient is upright small high-density pellets sink to the bottom of the stomach where they become entrapped in the folds of the antrum and withstand the peristaltic waves of the stomach wall. A density close to 2.5 g /cm^3 seems to be necessary for significant prolongation of gastric residence time and barium sulphate, zinc oxide, iron powder, titanium dioxide are used as excipients.

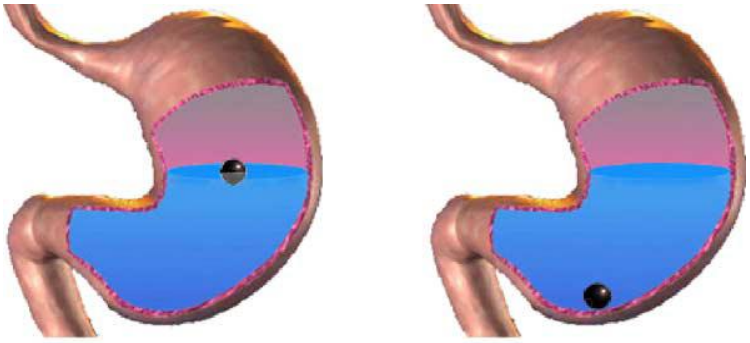


Fig:1 Schematic localization of an intragastric floating system and a high-density System in the stomach

3. Expandable systems

A dosage form in the stomach will withstand gastric transit if it is bigger than the pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, three configurations are required: a small configuration for oral intake, an expanded gastroretentive form and a final small form enabling evacuation following drug release. Unfoldable and swellable systems have been investigated. Unfoldable systems are made of biodegradable polymers. The concept is to make a carrier, such as a capsule, incorporating a compressed system which extends in the stomach.

4. **Hydrogel systems**

Although these are swellable systems, they differ sufficiently from the conventional types to warrant separate classification. With pore size ranging between 10 nm and 10 Am, absorption of water by conventional hydrogel is a very slow process and several hours may be needed to reach an equilibrium state during which premature evacuation of the dosage form may occur. Superporous hydrogels, average pore size >100 Am, swell to equilibrium size within a minute, due to rapid water uptake by capillary wetting through numerous interconnected open pores Moreover, they swell to a large size and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction.

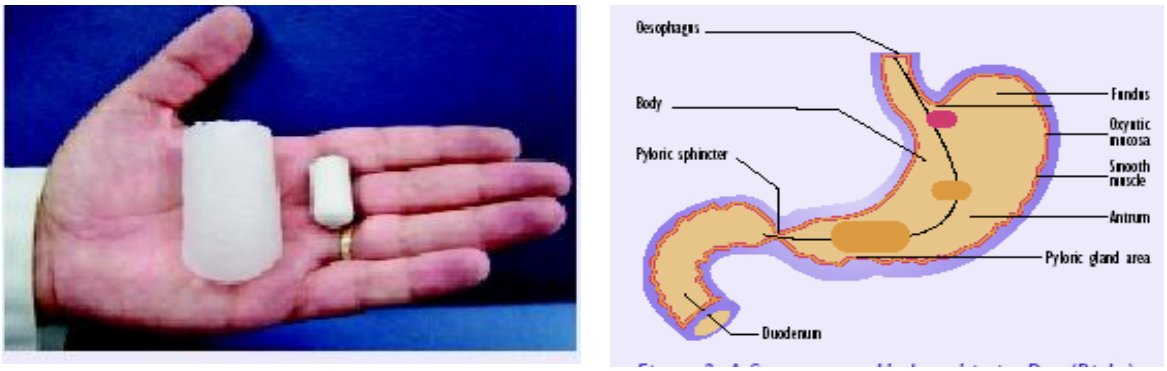


Fig: 2 i) On the left, superporous hydrogel in its dry (a) and water-swollen (b) state. ii) On the right, schematic illustration of the transit of superporous hydrogel.

5. Mucoadhesive or bioadhesive systems:

The basis of mucoadhesion is that a dosage form can stick to the mucosal surface by different mechanisms. Different theories are invoked to explain these mechanisms. Firstly, the electronic theory proposes attractive electrostatic forces between the glycoprotein mucin network and the bioadhesive material. Secondly, the adsorption theory suggests that bioadhesion is due to secondary forces such as Van der Waals forces and hydrogen bonding. The wetting theory is based on the ability of bioadhesive polymers to spread and develop intimate contact with the mucus layers, and finally, the diffusion theory proposes physical entanglement of mucin strands and the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate. Materials commonly used for bioadhesion are poly(acrylic acid)

(Carbopol\, polycarbophil), chitosan, Gantrez\ (Polymethyl vinyl ether/maleic anhydride copolymers), cholestyramine, tragacanth, sodium alginate, HPMC, sephadex, sucralfate, polyethylene glycol, dextran, poly(alkyl cyanoacrylate) and polylactic acid.

6. Magnetic systems:

This system is based on a simple idea: the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Although these systems seem to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance.

1.4 Technological developments in FDDS: [1, 5, 6, 9]

Based on mechanism of buoyancy, two distinctly different technologies have been utilized in the development of FDDS, which are effervescent system and non effervescent system.

A. Effervescent system:

Effervescent system include use of gas generating agents, carbonate(sodium bicarbonate) and other organic acids (citric acid and tartaric acid) to produce carbon dioxide(CO_2) gas, thus reducing the density of the system and making it to float on the gastric fluid. The effervescent further classified into two types.

(I) Gas Generating Systems:

1. Intra Gastric Single Layer Floating Tablet:

These are formulated by the CO_2 generating agents and the drug within matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in GRT and better control over fluctuations in plasma drug concentrations.

2. Intra Gastric Bilayered Floating Tablets:

These are also compressed tablets and contain two layers for:

Immediate release layer and Sustained release layer

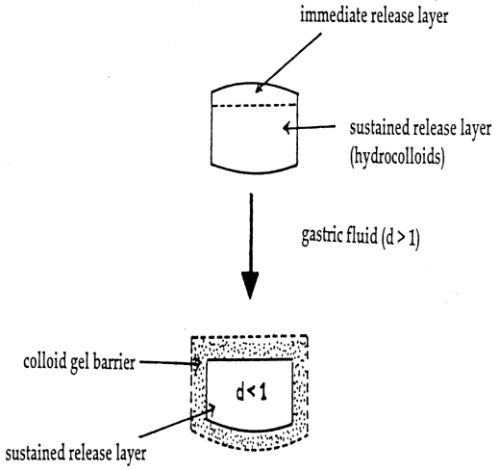


Fig: 3 Intra Gastric Bilayered Floating Tablets

3. Multiple Unit type floating pills:

These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature it sinks at once and then forms swllowen pills like balloon and float as the density decreases.

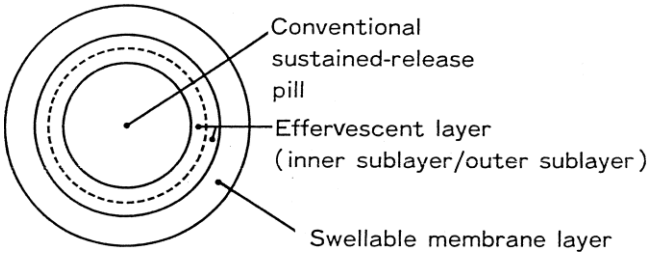


Fig: 4 A multiple-unit oral floating dosage system.

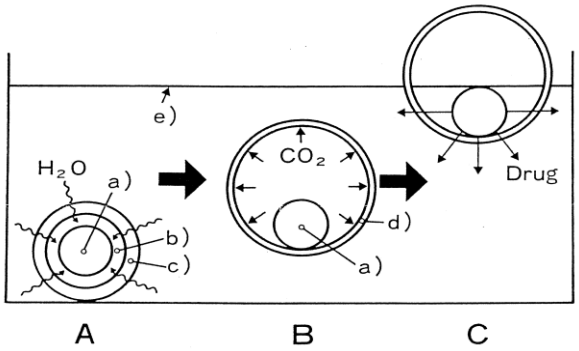


Fig: 5 Stages of floating mechanism: (A) penetration of water; (B) generation of CO_2 and floating; (C) dissolution of drug. Key: (a) conventional SR pills; (b) effervescent layer; (c) swellable layer; (d) expanded swellable membrane layer; (e) surface of water in the beaker

II. Volatile liquid/ vacuum containing systems:

1. Intragastric Floating Gastroretentive Drug Delivery System:

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporous compartment.

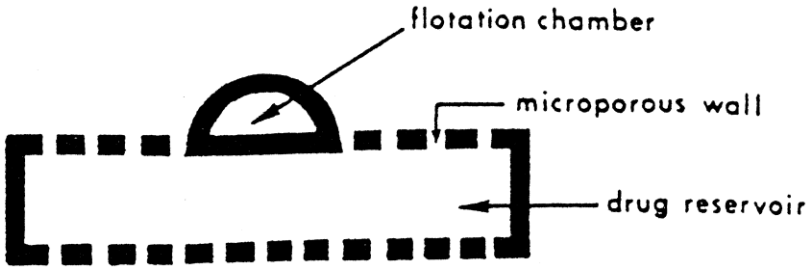


Fig6: Intragastric floating drug delivery device

2. Inflatable Gastroretentive Delivery System:

In these systems an inflatable chamber is incorporated, which contains liquid that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, impregnated polymeric matrix, and then encapsulated in a gelatin capsule. After oral administration of the capsule dissolve to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically

inflates and retains the drug reservoir compartment in floating position. The drug continuously released from the reservoir into the gastric fluid.

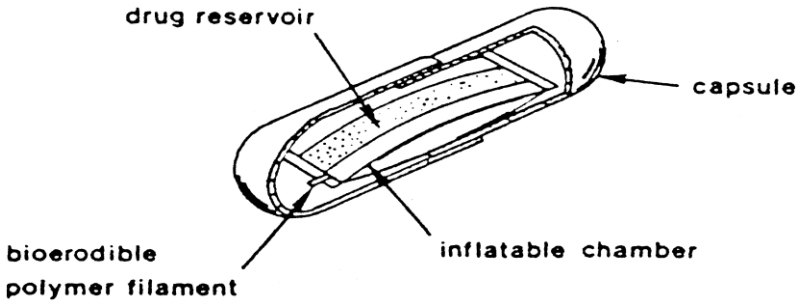


Fig: 7 Gastro-inflatable drug delivery device

3. Intragastric Osmotically Controlled Drug Delivery System:

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment.

The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and turns in forces the drug reservoir compartment reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release in solution form through the delivery orifice.

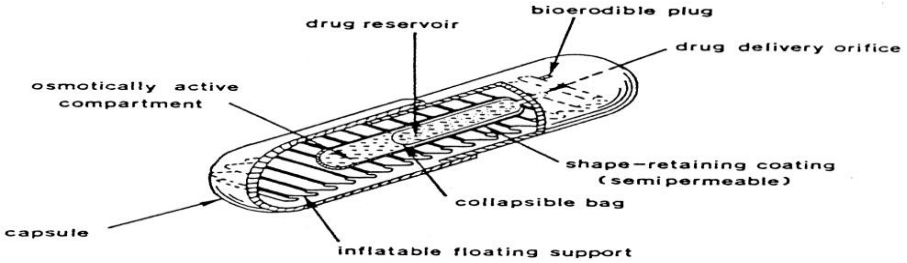


Fig: 8 Intragastric osmotic controlled drug delivery system

B. Non Effervescent Systems: [2, 7]

The non effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming materials such as polycarbonates, polyacrylates, polymethaacrylates, polystyrenes etc. and bioadhesive polymer such as chitosan and carbopol.

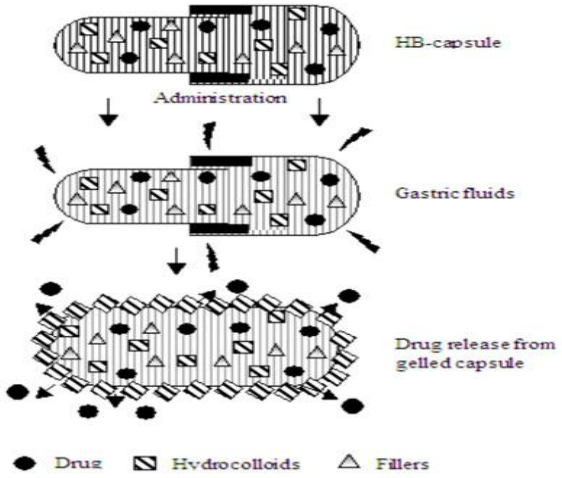


Fig: 9 Principle of hydrodynamically balanced system.

The various types of systems are:

- **Single Layer Floating Tablets:**

They are formed by intimate mixing of drug with a gel forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

- **Alginate Beads:**

Multi unit floating dosage forms were developed from freeze dried calcium alginate. Spherical beads of approximately 2.5mm diameter can be prepared by dropping sodium alginate into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hr. These floating beads gave a prolonged residence time of more than 5.5 hr.

- **Hollow Microspheres:**

Multiple-unit hollow microspheres by emulsion solvent diffusion technique were prepared with drug and acrylic polymer. These were dissolved in an ethanol-dichloromethane

mixture, and poured into an aqueous solution of PVA with stirring to form emulsion droplets. The rate of drug release in micro balloons was controlled by changing the polymer to drug ratio. Microballons were floatable in vitro for 12 hours when immersed in aqueous media. Radio graphical studies proved that microballons orally administered to humans were dispersed in the upper part of the stomach and retained there for 3 hours against peristaltic movements.

1.5 Advantages and Disadvantages of FDDS[7, 10]

Advantages of FDDS:

- Drugs that act locally in the stomach e.g. antacids, antibiotics for microbial based ulcer, etc.
- Drugs that are absorbed primarily in the stomach e.g. Albuterol
- Drugs those are poorly soluble in alkaline pH.
- Drugs that have narrow absorption window for absorption of the drugs which are absorbed from the proximal part of the small intestine. E.g. riboflavin, Levodopa, PABA.
- Drugs that degrade in colon e.g. Captopril, Metoprolol.

Disadvantages of FDDS:

- High variability in gastric emptying time due to variations in emptying process.
- Drugs that cause irritation and leisions to gastric mucosa and unstable in gastric fluid cannot be formulated as FDDS
- Drugs with unpredictable bioavailability, minimum effective concentration are achieved slowly.
- Gastric retention is achieved by many factors such as gastric motility, pH, and presence of food. These factors are never constant hence the buoyancy cannot be predicted.

Table N0.1: MARKETED PRODUCT OF FDDS:

Sr. No.	Brand Name	Delivery system	Drug (dose)	Company, Country
1	Madopar	Floating, CR capsule	Levodopa (100 mg), Benserazide (25 mg)	Roche Products, USA
2	Valrelease	Floating capsule	Diazepam (15 mg)	Hoffmann-LaRoche, USA
3	Liquid Gaviscon	Effervescent floating liquid alginate preparation	Al hydroxide (95mg), Mg carbonate (358 mg)	Glaxo Smith-Kline, India
4	Topalkan	Floating liquid alginate preparation	Al-Mg antacid	Pierre Fabre Drug, France
5	Almagate Flot Coat	Floating dosage form	Al-Mg antacid	----------
6	Conviron	Colloidal gel forming FDDS	Ferrous sulphate	Ranbaxy, India
7	Cifran OD	Gas-generating floating form	Ciprvenlafaxine hcl (1g)	Ranbaxy, India
8	Cytotec	Bilayer floating capsule	Misoprostol (100mcg/200mcg	Pharmacia, USA

Depression: [12, 13]

- It is an affective disorder which refers to a change in mood state. It is characterized by symptoms like loss of interest, suicidal thoughts, low energy change in appetite and sleep.
- One in four men and one in six men will suffer from depression at some point in their lives. It is a complicated illness which involves a number of contributing factors – genes, environment, diet, lifestyle, psychology and personality.
- For treatment of depression based on patient individual symptoms various antidepressants are used include MAO's, TCA's, SSRI's which are associated with major side effects.
- Venlafaxine HCl is a novel antidepressant of serotonin and noradrenaline reuptake inhibitor with prominent side effects are sweating, anxiety, dizziness and impotence. But doesn't interact with adrenergic, cholinergic, histaminic receptors thus having
    - No sedative action
    - Fast onset of action
    - Safer in overdose
    - No usual side effects

CHAPTER II

REVIEW OF LITERATURE

2. REVIEW OF LITERATURE ON FLOATING DRUG DELIVERY SYSTEM

Anil G *et al.*, (2011), prepared a controlled release tablet of Venlafaxine HCl, which releases the drug in a sustained manner over a period of 12 hrs. Three different viscosity grades of HPMC namely K4M, K15M, K100M were used for the tablets. The tablets were prepared by direct compression method and then evaluated. A combination of HPMC k100M was found to achieve optimum *in-vitro* buoyancy.[16]

Senthil A *et al.*, (2011), formulated the mucoadhesive microspheres of Venlafaxine HCl by single emulsification phase separation technique using different volumes of glutaraldehyde as crosslinking agent. The optimized formulation was selected based on the percentage of mucoadhesion and sphericity of microspheres.the optimized formulation exhibited a high drug entrapment efficiency of 70% and a swelling index 1.57%.Mucoadhesion after 1 hr was 91% and the drug release was also sustained for more than 12hrs. As the concentration of the glutaraldehyde increased, the mucoadhesiveness decreases and there was no significant effect in time.[17]

Pare. A *et al.*, (2011), developed amlodipine besylate effervescent floating tablets by using hydrophilic polymers HPMC and cabopol934 along with effervescent agents like sodium bicarbonate and citric acid. It was found that carbopol has a negative effect on floating behavior but it was found that carbopol has a negative effect on floating behavior but it was used only for the drug release retardant charecteristics.[18]

Sreekanth S.K. *et al.*, (2010), prepared floating matrix tablets using HPMC K100M as a polymer and sodium bicarbonate as gas generating agent. The compressed were then evaluated and there was no interaction between drug polymer and excepients, it was found out by IR studies. The *in-vitro* drug release study indicate that the release of the drug depends on the proportion of the polymer present in formulation .As the polymer ratio increases the release rate of the drug is prolonged.[19]

Subash C *et al.*, (2011), designed a controlled release floating tablet of Diltiazem HCl using Xanthan gum as a polymer. It was noted that the drug release from the prepared tablets was found to vary with varying concentration of the polymer. From the study it was concluded that floating tablets can be prepared by using Xanthan gum as a carrier.[20]

Bagherwal A *et al.*, (2010), have formulated the floating tablets of Ciprofloxacin HCl with HPMC and carbomer in different proportions (4%, 8%,9 %) by direct compression technique. The formulations were then evaluated and the mechanism of drug release with all the formulations was dominantly diffusion and followed zero order kinetics. The results revealed the drug polymer ratio showed greater drug release than other formulations.[21]

Raja *et al.*, (2011), prepared a gastro retentive floating tablets of Glipizide by using two different polymers HPMC K4M and HPMC K15M at different concentration. It was found that as the concentration of polymer increased, floating lag time decreased. Use of high viscosity polymer can also decreases the floating lag time and viscosity of the polymer should directly proportional relationship with swelling characteristics of tablets.[22]

Kotwal K *et al.*, (2008), prepared intragastric buoyant tablets of Amoxicillin trihydrate by using different grades of HPMC polymer as gelling agent. It was found that hardness of the tablet will affect the buoyancy characteristics of the dosage form. The in-vitro release study was concluded that amoxicillin releases from the tablet followed peppa's model with non-fickian diffusion.[23]

Patel VM *et al.*, (2009), were prepared gastroretentive tablets of Verapamil HCl by using different hydrocolloid polymer including carbopol (CP 934; CP 940), hydroxypropaxymethylcellulose (HPMC K4M; HPMC K15M; HPMC E15) and xanthan gum by direct compression technology. The selected tablets containing xanthan gum released approximately 97.89% drug in 24 hours *in-vitro* dissolution study, while buoyancy lag time was 24.6 seconds and the tablet remained buoyant for more than 24 hours. [24]

Jaimini M *et al.*, (2007), were formulated Famotidine floating tablets by using different grades of methocel (K100, K15M), PVP K-30, gas generating agent sodium bicarbonate and citric acid. The floating tablets were evaluated for physicochemical characteristics. All the prepared batches showed good *in vitro* buoyancy. The effect of citric acid on drug release profile and floating properties was investigated. The tablets with methocel K100 were found to be float for longer duration as compared with formulation containing methocel K15.[25]

Prabhu P *et al.*, (2008), were prepared a gastro retentive floating controlled drug delivery system containing Glipizide in the form of tablet. Ten formulations containing retardant materials such as HPMC4K and eudragit RS100, alkalizing agent sodium bicarbonate and other release promoters such as sodium lauryl sulphate and polyvinyl pyrrolidone were used. Tablets remained buoyant over 8 hours in the release medium, and the amount of sodium bicarbonate found to be significant for not only to remaining buoyant without causing disintegration of the tablet. Further the selected best formulations were compared with the marketed sustained release product and found to be comparable release of the drug. All the formulations exhibited diffusion dominated drug release.[26]

Deshmukh VN *et al.*, (2009), were prepared theophylline anhydrous bioadhesive tablets by using different natural polymers such as xanthan gum, locust bean gum, guar gum, karaya gum and their combinations were used to formulate matrix tablets. The bioadhesive strength of the tablets were measured as the force of detachment against the porcine gastric mucosa. The combination of karaya gum: guar gum (6:4) Tablet showed greater biodhesive strength as compared with single gum and other gum combination tablets. Karaya gum: guar gum loaded tablets were not discharged from the mucous membrane and were dissolved in gastric fluid. An increase in the gum concentration increases the drug profile beyond 12 hours whereas there is no significant effect of gum concentration on bioadhesive strength of the tablet.[27]

Rahman *et al.*, (2006), designed the bilayer floating tablets of captopril using HPMC-K15 M, K4M, PVP-K30 and Carbopol 934p alone or in combination with the drug in release layer and HPMC K grade, effervescent mixture of citric acid and sodium bi carbonate in the floating layer. It was found that 95 % of drug released in 24 hrs, tablet remained floatable throughout all studies and release followed the Higuchi model. In vivo X-ray studies indicated that placebo formulation containing barium sulphate in the release layer significantly increased the gastric residence time.[28]

Gambhire *et al.*, (2007), Studied on Oral floating matrix tablets of Diltizem Hydrochloride by using Methocel K-100M CR, Compritol 888 ATO, Sodium bicarbonate, succinic acid and concluded that the effervescent-based floating drug delivery is a promising approach to achieve *in vitro* buoyancy by using gel-forming polymer methocel K 100 CR and gas generating agent sodium bicarbonate. A high level of both Methocel K-100M CR and compritol 888 ATO favors the preparation of the floating controlled release of DTZ tablets.[29]

Arza RAK *et al.*, (2009), were prepared Swellable and floating gastroretentive ciprofloxacin hydrochloride tablet by using a combination of hydrophilic polymer (hydroxypropylmethylcellulose), swelling agent (crosspovidone, sodium starch glycolate, and croscarmelose sodium) and effervescent substance (sodium bicarbonate). A combination of HPMC K100, crosspovidone, and sodium carbonate shows the good swelling, drug release, and floating character than the marketed product of ciprofloxacin hydrochloride CIFRAN OD.[30]

Prajapati ST *et al.*, (2009), were prepared Floating matrix tablets of domeperidone were prepared by wet granulation technique, using polymer such as HPMC K4M, carbopol 934P and sodium alginate either alone or in combination, and other standard excipients. Tablets were evaluated for physical characteristics and *in vitro* release characteristics for 24 hours. Floating matrix tablet based on combination of three polymers exhibited desired floating and prolonged drug release for 24 hours. Carbopols loading showed negative effect on floating properties but were found helpful to control the release rate of drug.[31]

Sungthongjeen S *et al.*, (2008), were designed Floating multi-layer coated tablets of theophylline based on gas formation. The system consists of a drug containing core tablet coated with a protective layer (hydroxypropylmethylcellulose), a gas forming layer (sodium bicarbonate) and a gas-entrapped membrane, respectively. The properties of acrylic polymers (eudragit RL 30D, RS 30D, NE 30D) and ethyl cellulose were characterized by the puncture test in order to screen a suitable film for the system. Eudragit RL 30D was chosen as a gas-entrapped membrane due to its high flexibility and high water permeability. The obtained tablets enabled to float due to the CO_2-gas formation and the gas entrapment by polymeric membrane.[32]

Singh S *et al.*, (2007), were developed floating matrix tablets of metoclopramide hydrochloride using the polymers such as guar gum, karaya gum, HPMC E15 alone and in combination with HPMC K15M (HK) and gas generating agents such as calcium carbonate and citric acid. Tablets with gas generating agent and with HK floated for 24 hours without complete erosion and showed slower drug release. This indicates that the gas forming agent contributes towards the initial floating of tablets and faster drug release and HK for maintaining the integrity of the floating matrix tablet and sustaining the drug release.[33]

Vinay pandit et al., (2010), designed gastro retentive form of amoxicillin trihydrate floating tablets. The formulations were prepared as matrix tablets in the form of non effervescent tablets by using various grades of HPMC. The granules were prepared by wet granulation technique and tablets were evaluated. The optimized formulation of amoxicillin was found to have increased gastric residence prolonging the release of drug with 85% of drug release in 6 hrs by diffusion. The mechanism of drug release was found to be diffusion and followed combination of zero order and first order kinetics.[34]

Mokhopadhayats et al., (2010), formulated floating bioadhesevie tablets of ciprofloxacin Hcl by direct compression technique. Tablets were prepared by using polymers like HPMC, SCMC, carbopol in different ratios. The effervescent base was prepared by using 1: 1 ratio of sodium bycarbonate and citric acid. It was observed that tablets with 5% effervescent base shows greater control in drug release in comparison to that of 10%.[35]

Atul kumar sahu et al., (2011), prepared buoyant controlled release tablet of furosemide containing chitosan and HPMC as a polymer and evaluated. The effect of chitosan and HPMC concentration on drug release kinetics and buoyancy was also determined. The in vitro drug release of furosemide in all the formulations was best explained by zero order equation and followed mechanism of non-fickian diffusion. By combining HPMC with chitosan in various blends, the formulation found to be more suitable for oral controlled release of furosemide.[36]

Srinivas reddy et al., (2010), developed floating matrix tablets of captopril by using natural gumd like xanthine gum, karaya gum, gellan gum along with HPMC K4M, PVP K30. The tablets were prepared by direct compression using sodium bicarbonate as gas generating agent and evaluated. The linear regression analysis and model fitting showed that all this formulation followed Higuchi model.[37]

CHAPTER III

DRUG AND EXCIPIENT PROFILE

3. DRUG AND EXCIPIENT PROFILE

3.1 DRUG DATA- VENLAFAXINE HCL: [14, 15]

Venlafaxine HCl is a serotonin and norepinephrine reuptake inhibitors

Molecular formula: $CH_{27}NO_2$ HCl

Molecular weight: 313.87

Structure:

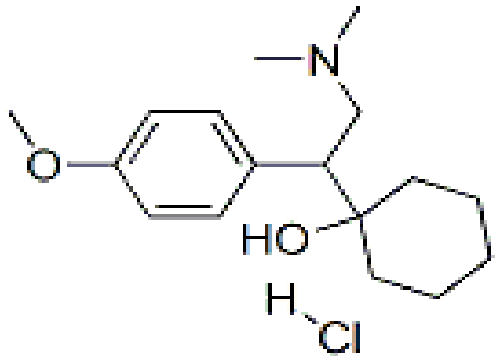


Fig: 10 Structure of Venlafaxine HCl

Chemical name: (*RS*)-1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]cyclohexanol

Category: Anti-depressant

3.1.1Physico-chemical properties:

Description: white crystalline powder

Standards: venlafaxine HCl contains not less than 98.5 per cent and not more than of 101.5 per cent , calculated on the dried basis.

Solubility: venlafaxine HCl is considered to be soluble in aqueous solutions with pH between 2 and 5. It is sparingly to slightly soluble in aqueous solutions with pH 7.

Melting point: Venlafaxine HCl melts at 207-209^{0}C

Bioavailability: 30%

Metabolism: Hepatic

Half life: 4hours

Excreation: Renal

Mechanism of action:

The mechanism of the antidepressant action of Venlafaxine HCl in humans is believed to be associated with its potentiation of neurotransmitter activity in the CNS. Preclinical studies have shown that Venlafaxine HCl and its active metabolite, O-desmethyl venlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Venlafaxine HCl and ODV have no significant affinity for muscarinic cholinergic, H1-histaminergic, or α1-adrenergic receptors in vitro. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Venlafaxine HCl and ODV do not possess monoamine oxidase (MAO) inhibitory activity.

Dosage and Administration:

Extended release:

Daily dose: 75-150 mg orally
Maximum dose (moderately depressed outpatients): 225 mg/day
Maximum dose (severely depressed inpatients): 375 mg/day

Adverse effects:

Suicidal thinking(suicidality), sweating, nausea, constipation, anorexia, vomiting, somnolence, dry mouth, dizziness, nervousness, anxiety, tremor, and blurred vision.

Contraindications:

Venlafaxine HCl hydrochloride tablets must not be used concomitantly in patients taking MAOIs or in patients who have taken MAOIs within the preceding 14 days due to the risk of serious, sometimes fatal, drug interactions with SNRI or SSRI treatment or with other serotonergic drugs. These interactions have been associated with symptoms that include tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, rigidity, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma.

3.2 POLYMER PROFILE: [15]

3.2.1 CARBOPOL934

1. Nonproprietary Names:

BP: Carbomer

USPNF: Carbomer

JP: carboxyvinyl polymer

2. Synonyms:

Carboxypolymethylene , polyacrylic acid.

3. Functional Category:

Controlled release agent, stabilizing agent, viscosity enhancing agent, binding agent.

4. Applications in pharmaceutical formulation or technology:

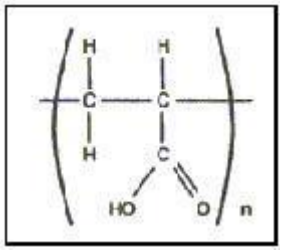
They are used in wide range of pharmaceutical applications which provide:

- Controlled release in tablets
- Bioadhesion in buccal, ophthalmic, intestinal, nasal, vaginal and rectal applications.
- Thickening at very low concentrations to produce a wide range of viscosities and flow properties in topical, lotions, creams and gels, oral suspensions and transdermal gel reservoirs.
- Permanent suspensions of insoluble ingredients in oral suspensions and topicals.
- Emulsifying topical oil-in-water systems permanently, even at elevated temperatures, with essentially no need for irritating surfactants.

5. Description:

It occurs as odorless, tasteless, fluffy white powder.

6. Structural Formula:



7. Solubility:

The Carbopol resins are hydrophilic substances that are not soluble in water. Rather, these polymers swell when dispersed in water forming a colloidal, mucilage-like dispersion.

Carbopol polymers are bearing very good water sorption property. They swell in water up to 1000 times their original volume and 10 times their original diameter to form a gel when exposed to a pH environment above 4.0 to 6.0.

8. Viscosity (dynamic):

Different grades of Carbopol polymers exhibit different rheological properties, a reflection of the particle size, molecular weight between crosslinks (Mc), distributions of the Mc, and the fraction of the total units, which occur as terminal, i.e. free chain ends. The viscosity range of different Carbopol polymers are as follows

S.No	polymer	viscosity
1	Carbopol 934 NF	30500 – 39400
2	Carbopol 934 p NF	29400 – 39400
3	Carbopol 71G NF	4000 – 11000

3.2.2 XANTHAN GUM

1. Nonproprietary Names:

BP: Xanthan gum

USPNF: Xanthani gum

2. Synonyms:

Corn sugar gum; E415; Keltrol; polysaccharide B-1459; Rhodigel; Vanzan NF; Xantural

3. Chemical Name:

Xanthan gum

4. Functional Category:

Stabilizing agent; Suspending agent; Viscosity-increasing agent.

5. Applications in pharmaceutical formulation or technology:

Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and foods as a suspending and stabilizing agent. It is also used as a thickening and emulsifying agent.

6. Description:

Xanthan gum occurs as a cream- or white-colored, odorless, free-flowing, fine powder.

7. Typical properties:

Acidity/alkalinity: pH = 6.0–8.0 for a 1% w/v aqueous solution.

Melting point : Chars at 270˚C.

Solubility : practically insoluble in ethanol and ether; soluble in cold or warm water

8. Safety: It is safe when up to 15grams per day are taken. It can cause some side effects such as intestinal gas.

3.2.3 HYDROXYPROPYL METHYLCELLULOSE

1. Nonproprietary Name:

BP: Hypromellose

USP: Hypromellose

2. Synonyms:

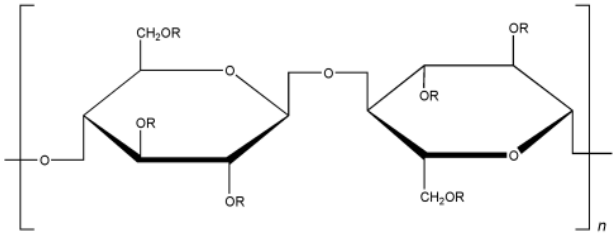
Hydroxy Propyl Methyl Cellulose, HPMC, Hypromellosum, Methocel, Methyl Cellulose Propylene Glycol Ether, Methyl Hydroxy Propyl Cellulose, Metolose, MHPC.

3. Chemical Name: Cellulose Hydroxy Propyl Methyl Ether

4. Empirical Formula and Molecular Weight:

The PhEur 6.3 describes hypromellose as a partlyO-methylated and O-(2-hydroxypropylated) cellulose. Molecular weight is approximately 10 000–1 500 000.

5. Structural Formula:



Where, R is H, CH_3, or $CH_3CH(OH)CH_2$

Fig: 11 Structure of HPMC

6. Applications in Pharmaceutical Formulation or Technology:

HPMC is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25–5.0%.

7. Description:

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

8. Solubility:

Soluble in cold water, forming a viscous colloidal solution, practically insoluble in hot water, chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane.

9. Viscosity (dynamic):

A wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared.

Typical viscosity values for 2% (w/v) aqueous solutions of methocel (Dow Chemical Co.) viscosities measured at 20ºC

Methocel grade	**Viscosity(cps)**
K4 M	4000
K15M	15000
K100M	100000

10. Stability and Storage Conditions:

Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

11. Safety:

Hypromellose is generally regarded as a nontoxic and nonirritating material, although excessive oral consumption may have a laxative effect.

3.3. EXCIPIENT PROFILE: [15]

3.3.1 SODIUM BICARBONATE

1. Nonproprietary Names:

BP: Sodium Bicarbonate

PhEur: Sodium Hydrogen Carbonate

USP: Sodium Bicarbonate

2. Synonyms:

Baking soda, E500, Effer-Soda, Sodium acid carbonate, Sodium hydrogen carbonate.

3. Chemical Name: Carbonic acid monosodium salt

4. Empirical Formula and Molecular Weight: $NaHCO_3$ and 84.01

5. Applications in Pharmaceutical Formulation or Technology:

Sodium bicarbonate is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules. It is also widely used to produce or maintain an alkaline pH in a preparation. Recently, sodium bicarbonate has been used as a gas-forming agent in alginate raft systems and in floating, controlled release oral dosage forms for a range of drugs. Therapeutically, sodium bicarbonate may be used as an antacid, and as a source of the bicarbonate anion in the treatment of metabolic acidosis.

6. Descriptions:

Sodium bicarbonate occurs as an odorless, white, crystalline powder with a saline, slightly alkaline taste.

7. Stability and Storage Conditions:

Sodium bicarbonate is stable in dry air but slowly decomposes in moist air and should therefore be stored in a well-closed container in a cool, dry place.

8. Incompatibilities:

Sodium bicarbonate reacts with acids, acidic salts, and many alkaloidal salts, with the evolution of carbon dioxide. Sodium bicarbonate can also intensify the darkening of salicylates.

9. Safety:

When used as an excipient, sodium bicarbonate is generally regarded as an essentially nontoxic and nonirritant material. Administration of excessive amounts of sodium bicarbonate may thus disturb the body's electrolyte balance, leading to metabolic alkalosis or possibly sodium overload with potentially serious consequences.

3.3.2 MICROCRYSTALINE CELLULOSE

1. Nonproprietary Names:

BP: Microcrystalline Cellulose

PhEur: Cellulose, Microcrystalline

USP-NF: Microcrystalline Cellulose

2. Synonyms: Avicel, cellulose gel, crystalline cellulose, E460, Emocel, Fibrocel, Tabulose, Vivacel.

3. Functional Category: Tablet and Capsule diluent, suspending agent, adsorbent, tablet disintegrant.

4. Applications: As a diluent in tablets (direct compression and direct compression) and capsule formulation. In addition to its use as a diluent, it also has some lubricant and disintegrant property.

5. Description: White-colored, odourless, tasteless crystalline powder composed of porous particles. Available in different particle size grades which have different properties and applications.

6. Solubility: Slightly soluble in 5 % w/v NaOH solution, practically insoluble in water, dilute acids and most organic solvents.

7. Stability: It is a stable, though hygroscopic material.

8. Storage conditions: The bulk material should be stored in a well-closed container in a cool and dry place.

9. Incompatibilities: Incompatible with strong oxidizing agents.

10. Safety: It is generally regarded as a nontoxic and nonirritant material.

3.3.4 MAGNESIUM STEARATE:

1. Non-proprietary names:

BP: Magnesium stearate

JP: Magnesium stearate

PhEur: Magnesii stearas

USPNF: Magnesium stearate

2. Synonyms: Magnesium octadecanoate, octadecanoic acid magnesium salt and stearic acid magnesium salt.

3. Chemical name: Octadecanoic acid magnesium salt

4. Structural formula: $[CH_3 (CH_2)_{16}COO]_2 Mg$

5. Molecular weight: 591.34

6. Functional category: Tablet and capsule lubricant.

7. Melting point: 117-150 ^0C

8. Description: Magnesium stearate is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to touch and readily adheres to the skin.

9. Solubility: It is practically insoluble in ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

10. Applications: It is widely used in cosmetics, foods and pharmaceutical formulations. It is primarily used as a lubricant in the manufacturing of tablets and capsules, in the concentration of 0.25-5.0%. It is also used in barrier creams.

11. Stability and storage conditions: It should be stored in a well closed container in a cool, dry place.

3.3.5 TALC

1. Non-proprietary names:

BP: Purified talc

PhEur: Talcum

USP: Talc

2. Synonyms: Altalc, powdered talc, purified French chalk, Purtalc, soapstone, steatite and Superiore.

3. Chemical name: Talc

4. Structural formula: $Mg_6 (Si_2O_5)_4(OH)_4$

5. Functional Category: Anticaking agent, glidant and lubricant.

6. Description:

It is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to touch and free from grittiness.

7. Solubility:

It is practically insoluble in dilute acids and alkalis, organic solvents and water.

8. Applications:

It was once widely used in oral solid dosage formulations as a lubricant and diluent. It is widely used as dissolution retardant in the development of controlled release products. In topical preparations, it is used as a dusting powder, although it should not be used to dust surgical gloves. It is a natural material it may frequently contain micro-organisms and should be sterilized when used as a dusting powder. It is additionally used to clarify liquids and is also used mainly for its lubricant properties, in cosmetics and food products.

9. Stability and storage conditions:

It is a stable material and may be sterilized by heating at 160°C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. It should be stored in a well closed container in a cool and dry place.

10. Incompatibilities:

It is incompatible with quaternary ammonium compounds.

CHAPTER IV

AIM & OBJECTIVES

4. AIM AND OBJECTIVE

4.1 AIM OF THE WORK

- The aim of this present work is to formulate a gastro retentive floating tablet of Venlafaxine HCl by direct compression method using various polymers such as Carbopol 934, Xanthan gum**,** and HPMC K-100M.
- Venlafaxine HCl exhibits pH dependent solubility. It is more soluble in acidic pH and slightly soluble at neutral or alkaline condition (intestinal environment). Hence an attempt will be made to develop gastroretentive delivery system of Venlafaxine HCl which would increase the bioavailability of Venlafaxine HCl and also to reduce frequency of administration, thereby improving patient compliance and therapeutic efficacy.

4.2 PLAN OF WORK

1. Pre- formulation studies for possible drug or polymer interaction by IR analysis.
2. Preparation of floating tablets by direct compression method.
3. Evaluation of the various properties of floating tablets.
    - Evaluation of precompression parameters such as bulk density, tapped density, compressibility index etc.
    - Evaluation of post compression parameters like thickness, hardness, friability, drug content, *In vitro* buoyancy studies.
4. Drug release study using suitable *in-vitro* model.
5. Carry out short term stability studies on the most satisfactory formulation.

CHAPTER V

METHODOLOGY

5. METHODOLOGY

5.1: INGREDIENTS USED:

Table No.2

S. No.	INGREDIENTS AND REAGENTS	MANUFACTURER / SUPPLIERS
1	Venlafaxine HCl	Aurabindo pharma
2	Carbopol 934p	Himedia laboratories
3	Xanthan gum	Himedia laboratories
4	HPMC K100M	Aurabindo pharma
5	Sodium bicarbonate	Nice laboratories
6	MCC	S.D fine chemicals
7	Magnesium Stearate	S.D fine chemicals
8	Talc	Nice laboratories

5.2 INSTRUMENTS USED:

Table No.3

Sr. No.	NAME OF INSTRUMENT	MANUFACTURING COMPANY
1.	Digital Balance	Shimatzu LB 300
2.	Tablet hardness tester	Pfizer hardness tester
3.	Friability tester	Riche Pharma
4.	Vernier Caliper	Mitutoyo digimatic caliper
5.	Dissolution apparatus USP	Electrolab tablet dissolution apparatus
6.	Double beam UV Spectrophotometer	Shimatzu UV-1800
7.	Rotary tablet punching machine	Cadmach
8.	pH meter	Elico Ll120
9.	FT-IR Spectrophotometer	KBR press model M15

5.3 PREFORMULATION STUDIES [38]

Preformulation testing is an investigation of physical and chemical properties of drug substances alone and when combined with pharmaceutical excipients. It is the first step in the rational development of dosage form.

5.3.1 Compatibility studies (Fourier Transform Infrared Spectroscopic studies)

Table no. 4: Description and composition of formulation

S. no.	INGREDIENTS	FUNCTIONS
1	Venlafaxine hcl	Active ingredients
2	Carbopol	Polymer
3	Xanthan gum	Polymer
4	HPMC K-100M	Polymer

Procedure:

The drug-excipient interaction study was carried out using by KBr pellet method. To study the compatibility of various formulation excipients with Venlafaxine HCl, solid admixtures were prepared by mixing the drug with each formulation excipient separately in the ration of 1:1 and it was filled and characterized by using Fourier transform infrared spectroscopy (FT-IR).

5.3.2 UV- Spectrum Analysis of Drug

Venlafaxine HCl drug solution in pH 1.2(0.1N HCl) was scanned using UV-Spectrophotometer between the range 210-400nm using pH 1.2 as blank and the range of the drug was found to be 224nm.

5.4 STANDARD CURVE OF VENLAFAXINE HCL BY UV-SPECTROPHOTOMETER

Venlafaxine HCl can be estimated spectrometrically at 224 nm as it obeys Beer's – Lambert's law limit is the range of 2-20µg/ml.

100mg of Venlafaxine HCl was dissolved in 100ml of 0.1N HCl so as to get a stock solution of 1000 µg/ml concentration.10ml of stock solution was made to 100ml with 0.1N HCl thus giving a concentration of 100 µg/ml. Aliquot of standard drug solution ranging from 0.2ml to 1ml were transferred in to 10ml volumetric flask and were diluted up to the mark with 0.1N HCl. Thus the final concentration ranges from 2-10 µg/ml. Absorbance of each solution was measured at 224 nm against 0.1N HCl as a blank. A plot of concentrations of drug vs. absorbance was plotted.

5.5 PREPARATION OF VENLAFAXINE HCL FLOATING TABLETS.[39, 40, 41]

Floating matrix tablet were prepared by using direct compression technique with use of different polymer with varying concentration(1:1,1:1.5,1:2) i.e., drug to polymer ratio as shown in the above table. All polymer and drug were passed through sieve no.80 separately. Then drug were mixed for 10 min with polymers and other excipients in weight proportion as mentioned in the table. The powder blend was then lubricated by magnesium stearate and talc and this lubricated blend were subjected to compression into tablets using 10-mm flat-face on a 16 stationary rotary punching tablet machine.

Table no. 5: Composition of floating tablets of Venlafaxine HCl

Ingrediants(mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Venlafaxine HCl	75	75	75	75	75	75	75	75	75
Carbopol934	75	112.5	150	–	–	–	–	–	–
Xanthan gum	–	–	–	75	112.5	150	–	–	–
HPMC K100M	–	–	–	–	–	–	75	112.5	150
MMC	95	57.5	20	95	57.5	20	95	57.5	20
Sodium bicarbonate	70	70	70	70	70	70	70	70	70
Mg stearate	5	5	5	5	5	5	5	5	5
Talc	10	10	10	10	10	10	10	10	10

Average weight of tablets 330 mg.

5.6 EVALUATION PARAMETERS [44, 45]

5.6.1 Pre Compression Parameters

1. Bulk density (D_b):

It is the ratio of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured into graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume. Bulk density is expressed in gm/cc and is given by,

$D_b = M / V_o$ Where, D_b = Bulk density (gm/cc)

M =Mass of powder (g)

V_o = Bulk volume of powder (cc)

2. Tapped density (D_t):

Ten grams of powder was introduced into a clean, dry 100ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and tapped volume was read. It is expressed in gm/cc and is given by,

$D_t = M / V_t$ Where, D_t = Tapped density (gm/cc)

M = Mass of powder (g)

V_t = Tapped volume of powder (cc)

3. Angle of repose (θ):

It is defined as the maximum angle possible between the surface of pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height (h), above a flat horizontal surface on which a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of funnel. The angle of repose was then calculated using the formula,

$\theta = \tan^{-1}(h/r)$ where, θ = angle of repose

h = height of pile,

r = radius of the base of the pile.

Table No.6: Relation between the angle of repose (θ), and Flowability

Angle of repose (θ)	Flowability
<20	Excellent
20-30	Good
30-40	Passable
>40	Very poor

4. Carr's Compressibility Index:

An indirect method of measuring powder flow from bulk densities was developed by carr. The percentage compressibility of powder was a direct measurement of the potential powder arch or the bridge strength and stability. Carr's index of each formulation was calculated according to equation given below:

$$\%\text{compressibility} = \frac{D_f - D_o}{D_f} \times 100$$

Where, D_f = Tapped density

D_o = Bulk density

Table no.7 Relationship between % compressibility and Flowability

CARR'S INDEX (%)	TYPE OF FLOW
5-12	Excellent
12-18	Good
18-23	Fair to passable
23-35	Poor
35-38	Very poor
>40	Extremely poor

5.6.2: Post Compression Parameters

1. Thickness:

Control of physical dimension of the tablet such as thickness is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using vernier calipers. It is measured in mm.

2. Hardness:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling.The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in Kg/cm^2.Three tablets were randomly picked and hardness of the tablets was determined.

3. Friability:

Tablet strength was tested by using Roche Friabilater. 20 tablets were weighed and placed in the friabilator and operated at for 100 revolutions (4min), taken out and were dedusted. The percentage weight loss was calculated by reweighing the tablets. The % friability was then calculated by,

$$F = \frac{(W_{initial}) - (W_{final})}{(W_{intial})} \times 100$$

4. Weight variation:

Ten tablets were selected randomly from each batch were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double the percentage limit.

Table No.8 IP standards of uniformity of weight

Sl.No	Average weight of tablet	% of deviation
1	≤ 130 mg	±10
2	> 130 mg to <324 mg	±7.5
3	≥ 324 mg	±5

$$PD = \frac{(W_{avg}) - (W_{initial})}{(W_{avg})} X\,100$$

Where, PD = Percentage deviation,

W_{avg} = Average weight of tablet,

$W_{initial}$ = individual weight of tablet.

5. Swelling Index: [38, 46]

Measurement of swelling rate of the floating matrix tablet was carried to gain insight the observed phenomenon of drug release with the rates of polymer hydration. Swelling index of the dosage form is conducted by using USP dissolution apparatus-II in 900 ml of 0.1N HCl which is maintained at 37±0.5°C, rotated at 50 rpm. At selected regular intervals, the tablet was withdrawn and the excess water was blotted with tissue paper and the swelling index was calculated using following formula.

% Swelling Index = $\{(W_t) – (Wo)/ (Wo)\}$ x 100

Where, Wt = weight of the swollen tablet

Wo = initial weight of the tablet.

6. Buoyancy studies:

The *in-vitro* floating behavior (buoyancy) of the tablets was determined by floating lag time.The tablets were placed in 100 ml beaker containing 0.1 N HCl (pH 1.2). The floating lag time (time taken by the tablet to reach the surface) and total floating time (floating duration of the tablet) were determined.

7. Uniformity of drug content:

The drug content was performed to check the dose uniformity in the formulation. Randomly ten tablets were weighed and powered. A quantity equivalent to 100mg of Venlafaxine HClwas added in to a 100ml volumetric flask and dissolved in 0.1N HCI, shaken for 10 minutes and made up to the volume with 0.1N HCl. After suitable dilutions the drug content was determined by UV spectrophotometer at 224nm again blank.

8. *In-Vitro* release studies for floating tablets[47]

The drug release rate was determined using USP dissolution apparatus II. Dissolution media was 900ml of simulated gastric fluid (pH 1.2) maintained at 37± 0.1 ˚C and stirred at 50 rpm. Samples were withdrawn at suitable time intervals and compensated with fresh dissolution medium and assayed spectrophotometrically at 224nm in Shimadzu U.V. spectrophotometer. Samples were assayed in triplicate.

9. Kinetic analysis of *In-Vitro* release rates of floating tablets of Venlafaxine HCl

Several kinetic models have been proposed to describe the release charecteristics of a drug from matrix. The following three equations were used, because of their simplicity and applicability.

- **Equation 1**, the zero order model (Plotted as cumulative percentage of drug Vs time).
- **Equation2**, First order kinetic model (Log cumulative percent drug remaining Vs time).
- **Equation 3**, Higuchi‘s square root equation (plotted as cumulative percent drug release Vs square root of time).
- **Equation 4**, the korsmeyer peppas equation (plotted as Log cumulative percent drug release Vs Log time).

To study the relese kinetics of Venlafaxin HCl the release was fitted to the above four equations.

Table no. 9: Mechanism of Drug Release as per Korsmeyer Equation / Peppa's Model

S. No.	N Value	Drug release
1.	0.45	Fickian release
2.	0.45 <n <0.89	Non – Fickian release
3.	n> 0.89	Class II transport

10. Stability studies[49]

Stability studies of pharmaceutical products were done as per ICH guidelines. These studies are designed to increase the rate of chemical or physical degradation of the drug substance or product by using exaggerated storage conditions.

Method: Selected formulations were stored at different storage conditions at elevated temperatures such as $25^{o}C \pm 2^{0}C$ / 60% ± 5% RH, $30^{0}C \pm 2^{0}C$ / 65% ±5% RH and $40^{0}C \pm 2^{0}C$/ 75% ± 5% RH for 90 days. The samples were withdrawn at intervals of 30 days and checked for physical changes, hardness, friability, drug content, floating lag time and percentage drug release.

CHAPTER VI

RESULTS & DISCUSSION

6. RESULTS AND DISCUSSION

6.1. DETERMINATION OF λmax OF Venlafaxine Hcl IN ACID BUFFER (pH 1.2)

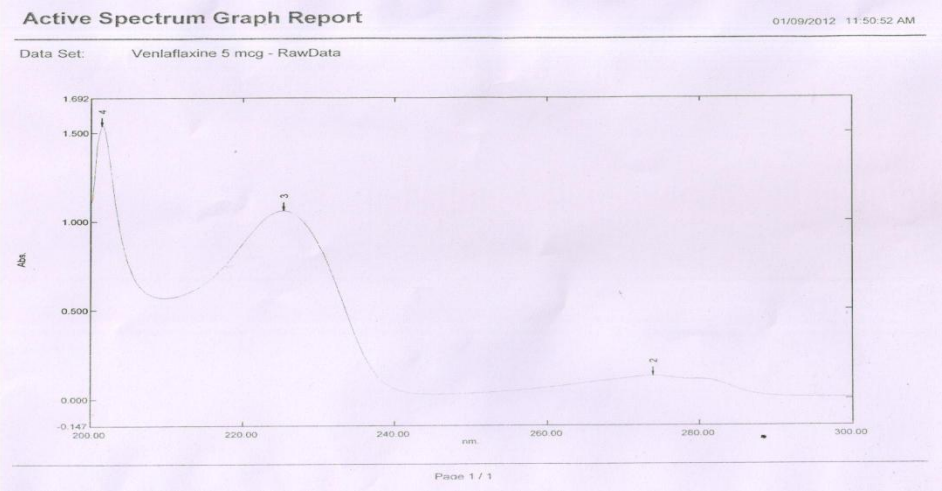


Fig12: Spectrum of Venlafaxine HCl

Venlafaxine HCl drug solution in pH 1.2(0.1N HCl) was scanned using UV-Spectrophotometer between the range 210-400nm using pH 1.2 as blank and the maximum absorbance (λ max) was found at **224nm.**

6.2. CALIBRATION CURVE OF Venlafaxine HCl

Table No.10: Calibration curve of Venlafaxine HCl in 0.1N HCl (pH 1.2)

Sl. No	Concentration(µg/ml)	Absorbance at 224nm
1	02	0.136
2	04	0.305
3	06	0.462
4	08	0.612
5	10	0.754

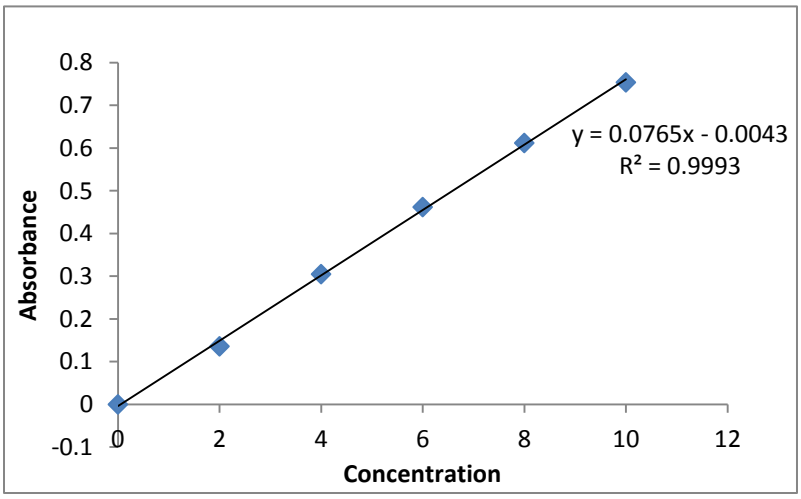


Fig13: Calibration curve of Venlafaxine HCl in 0.1N HCl (pH 1.2)

From the standard curve of Venlafaxine HCl it was observed that the drug obeys Beer's law in the range of 2-20µg/ml.

6.3 FTIR STUDIES

TABLE NO. 11 Compatibility Studies of Venlafaxine HCl with Excipients

SL. NO	Excipients	Drug/ Excipients Ratio	Physical Description Initial	$35^0C \pm 2^0C$ / 60% ± 5% RH		
				1 Week	**2 Week**	**3 Week**
1	Venlafaxine HCl	-	White crystalline powder	*	*	*
2	Drug + carbopol934	1:1	White crystalline powder	*	*	*
3	Drug + xanthan gum	1:1	White crystalline powder	*	*	*
4	Drug + HPMC k100M	1:1	White crystalline powder	*	*	*

*** indicates no incompatibility**.

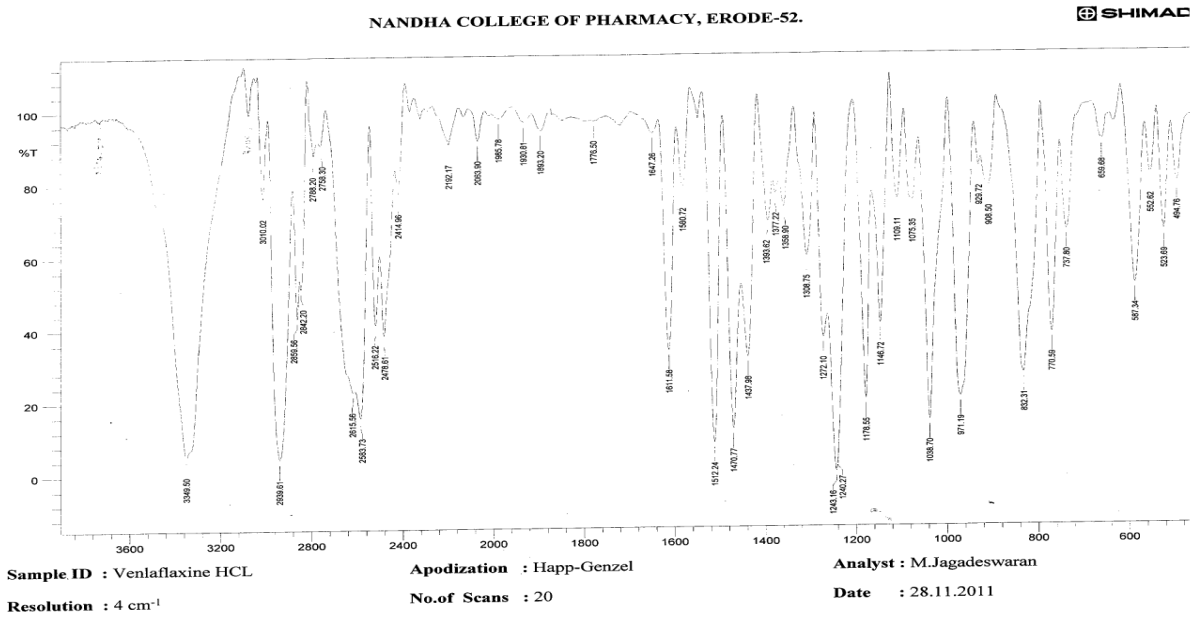


Fig14: FTIR Spectroscopy of pure drug

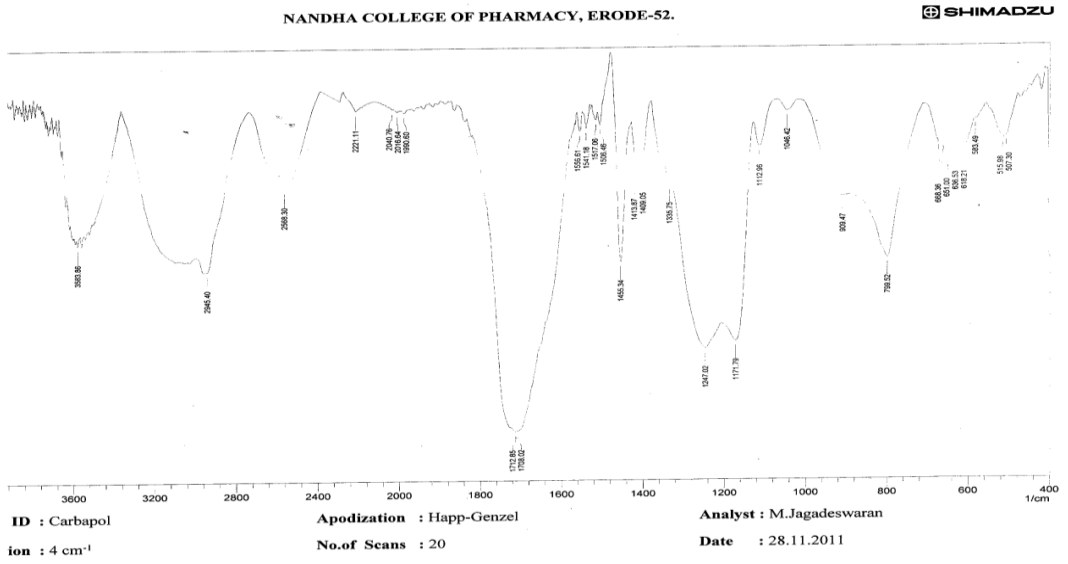


Fig15: FTIR Spectroscopy of Carbopol934

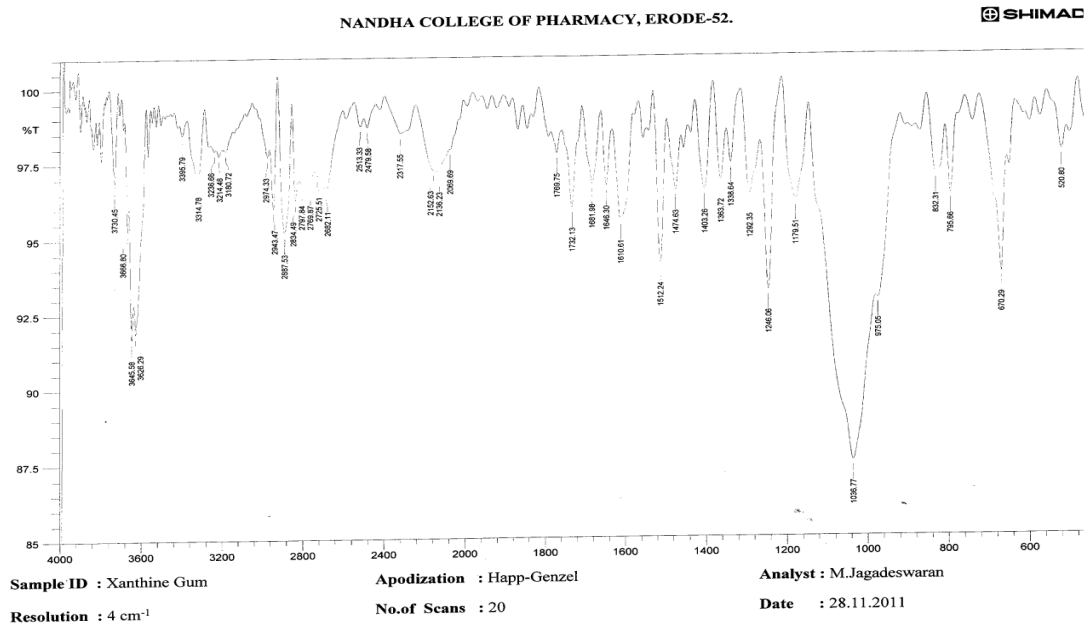


Fig16: FTIR Spectroscopy of Xanthan gum

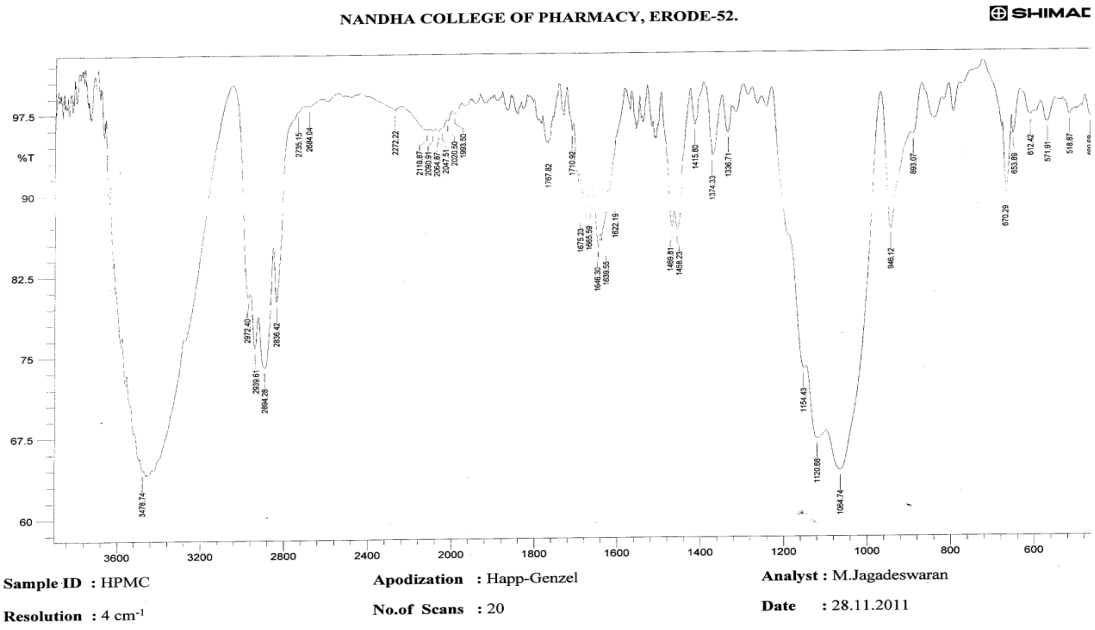


Fig17: FTIR Spectroscopy of HPMC K100M

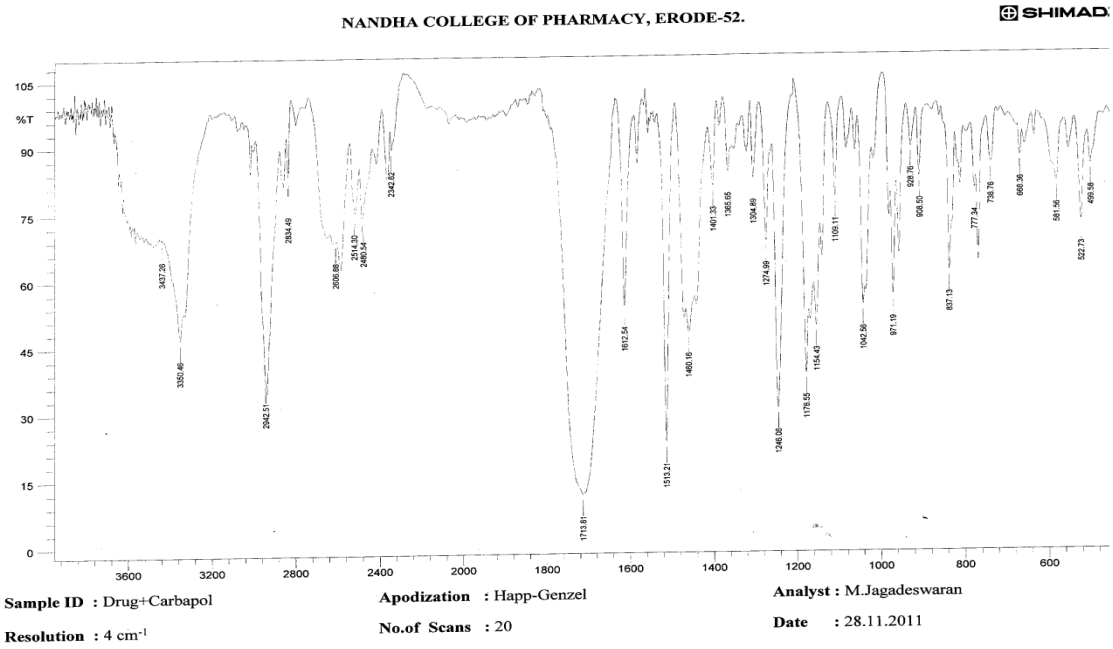


Fig18: FTIR Spectroscopy of pure drug+ Carbopol 934

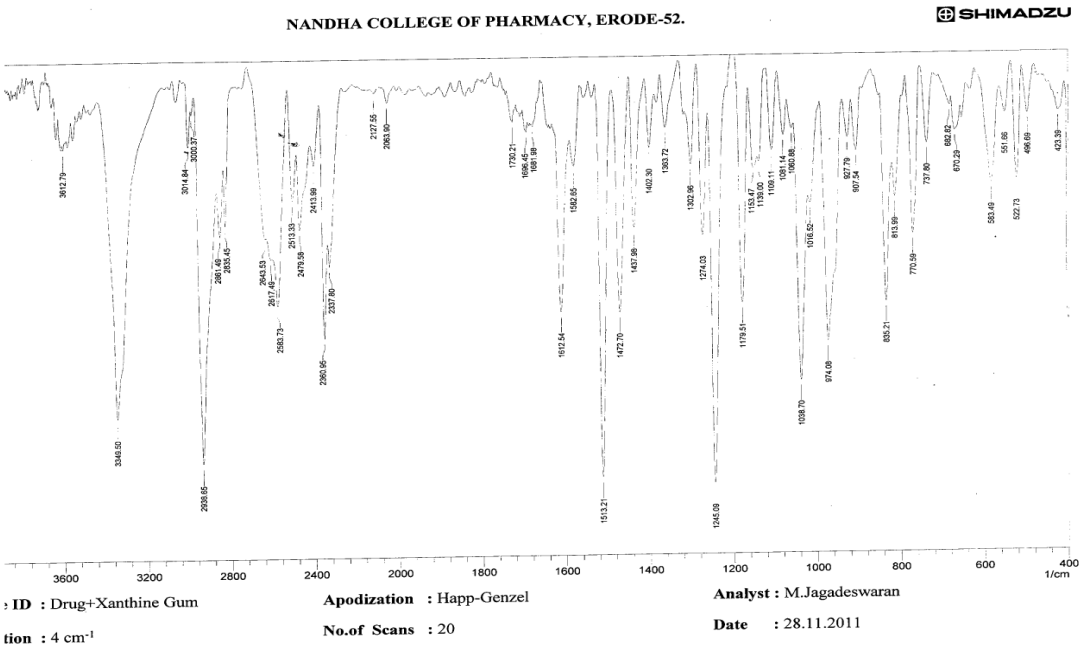


Fig19: FTIR Spectroscopy of pure drug+ Xanthan gum

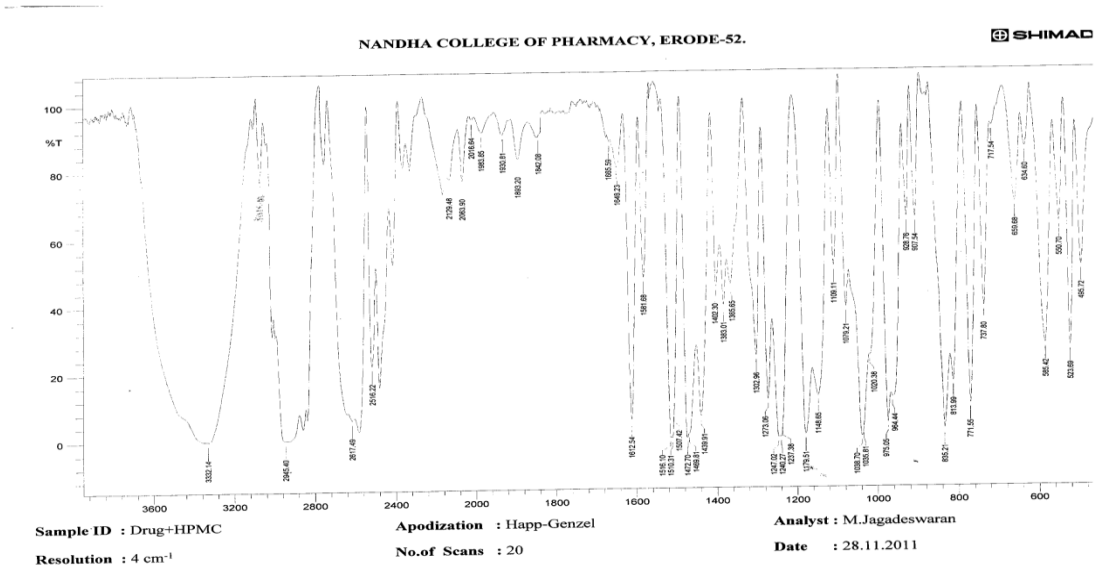


Fig20: FTIR Spectroscopy of pure drug+ HPMC K100M

Table No. 12: Comparison of the peak of functional groups of Venlafaxine HCl observed in IR spectra of compatibility studies:

S. No	Types of vibrations	IR absorption Ranges (cm^{-1})	Drug (cm^{-1})	Physical mixture(drug + polymer)		
				Drug + xanthan gum	Drug + carbopol 934	Drug + HPMC K100M
1	Aromatic C-H stretching	3000-2850	2939.6	2936.5	2942.5	2945.4
2	Aromatic C=C stretching	1680-1600	1647.2	1642.9	1632.4	1648.2
3	O-H stretching	3400-3600	3349.5	3349.5	3437.2	3332.1
4	C-O stretching	1300-1000	1243.16	1245.9	1246.6	1247.2
5	N-H stretching (1˚ & 2˚amine)	3500-3100	3349.5	3349.5	3437.2	3332.1
6	C-N stretching	1350-1000	1308.7	1302.9	1304.5	1302.9

- In order to check the integrity of the drug in the formulation, FTIR spectra of pure drug(Venlafaxine HCl), Carbopol 934, HPMC K100M, Xanthan gum and mixture of drug with the above polymers were taken and compared. The FTIR spectrum of Venlafaxine HCl reveal the presence of peaks at 2939.6 due to the presence of C-H stretching, 1647.2 due to the presence of C=C aromatic stretching, 3349.5 due to the presence of O-H stretching, 1243.16 due to the presence of C-O stretching, 3349.5 due to the presence of N-H stretching, 1308 due to the presence of C-N stretching.
- Major frequencies of functional groups of pure drug remain intact in powder containing Carbopol 934, HPMC K100M and Xanthan gum. Hence there is no major interaction between the drug and polymers used in the study.

6.4 EVALUATION PARAMETERS:

6.4.1 Pre Compression Parameters

Table No.13: Evaluation parameters of powder blend

Formulation	Angle of repose	Bulk density(gm/cc)	Tapped density(gm/cc)	Compressibility index (%)
F1	$29^{0}1^{1}$±0.1	0.36±0.004	0.41±0.018	11.8±0.8
F2	$30^{0}3^{1}$±0.2	0.37±0.001	0.44±0.017	13.4±0.8
F3	$32^{0}1^{1}$±0.5	0.38±0.005	0.44±0.004	13.3±0.6
F4	$30^{0}6^{1}$±0.3	0.35±0.005	0.41±0.003	14.2±1.4
F5	$32^{0}8^{1}$±0.5	0.34±0.004	0.40±0.018	14.8±1.2
F6	$33^{0}8^{1}$±0.1	0.35±0.002	0.42±0.001	16.2±0.7
F7	$28^{0}1^{1}$±0.7	0.35±0.002	0.40±0.005	12.6±0.9
F8	$28^{0}5^{1}$±0.3	0.36±0.003	0.41±0.002	12.7±1.1
F9	$31^{0}2^{1}$±0.1	0.36±0.005	0.42±0.004	14.2±1.3

- Floating tablets of Venlafaxine HCl was developed to increase the gastric residence time of the drug, so that they can be retained in the stomach for longer time and help in controlled release of drug up to 12 hrs.
- Different grades of viscosities of Carbopol 934, xanthan gum, HPMC K100M polymers is known to be beneficial in improving floating property and release charecteristics.
- The pre- compression parameters obtained for all formulations are tableted in the table no 13. The value of angle of repose was found to be in the range of $28^{0}1^{1}$ to $33^{0}8^{1}$. This indicates good flow property of powder blend. Carr's index value ranges between 11.8 to 16.2% indicates that the powder blend have the required flow property for direct compression.

6.4.2 Post Compression Parameters:

Table no.14: Evaluation parameters of formulations

Formulation	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Average weight variation(mg)	Drug content (%)
F1	3.76±0.04	5.33±0.02	0.65±0.07	331.2±1.3	98.06
F2	3.68±0.07	5.61±0.05	0.59±0.09	330.7±1.4	98.39
F3	3.62±0.02	5.44±0.03	0.53±0.05	331.5±1.7	97.22
F4	3.71±0.04	5.48±0.01	0.54±0.11	330.2±2.1	99.02
F5	3.67±0.09	5.86±0.04	0.47±0.08	329.8±2.3	97.18
F6	3.63±0.11	6.14±0.02	0.47±0.12	331.3±2.1	97.56
F7	3.74±0.02	5.42±0.03	0.57±0.04	329.2±1.4	97.19
F8	3.76±0.01	5.57±0.01	0.54±0.07	328.7±1.8	98.45
F9	3.69±0.05	5.72±0.05	0.53±0.06	331.4±1.2	98.28

- The floating tablets were prepared by direct compression method using the polymers Carbopol 934, Xanthan gum, HPMC K100M to provide sufficient drug release retardation and provide sufficient buoyancy to the tablets .The results have shown in the table no.14.
- The prepared floating tablets were evaluated for thickness, hardness, friability, average weight variation, drug content, all the studies were performed in triplicates and the results were expressed in ± standard deviation.
- The measured hardness for the tablets for each batch arranged between 5.33 to 6.14 kg/cm, this ensures the good handling characteristics of all the batches.
- The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.
- The weight variation for different formulations was found to be 328.7 to 331.4, indicates consistency in each batch.
- The drug content was found to be 97.19 to 98.45, with low standard deviation indicates batch to batch consistency.

6.5 SWELLING INDEX:

Table no.15: Swelling index (%) of formulations

Time (hrs)	Formulations								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	26.6	23.3	22.8	40.7	37.2	36.4	22.1	19.4	17.8
2	43.88	39.36	41.2	73.25	74.5	68	36.5	36.1	34.7
4	87.45	74.77	65.7	115.4	108.4	109.3	72.3	64.2	59.4
6	123.5	121.1	114.8	140.2	132.8	130.7	112.7	98.2	89.2
8	155.4	146.2	124.1	163.7	160.3	154.2	128.7	114.5	114.2
10	158.8	149.7	132.8				132.3	121.1	119.5
12	162.4	154.5	133.4				135.1	126.9	122.3

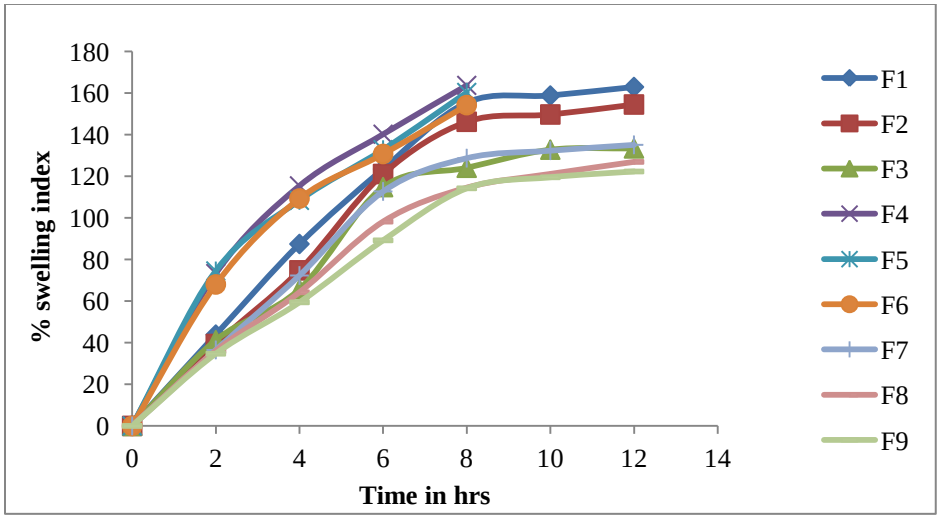


Fig21: Graph for comparison of swelling index of all the formulation

Swelling index for all the formulations was carried out in the 0.1N HCl. The formulations showed different indices in the swelling media and it is shown in the table. Tablets containing carbopol934 and HPMC K100M showed maximum swelling in 12 hr with sharp increase up to 8 hr this may due to increased concentration of HPMC K100M which retain water and form thick swollen mass.

6.6 BUOYANCY STUDIES:

Table no. 16: Buoyancy studies of formulations

Formulation code	Floating lag time (sec)	Floating duration (hrs)
F1	52	>12
F2	58	10
F3	76	10
F4	29	7
F5	36	8
F6	34	8
F7	34	>12
F8	32	>12
F9	39	>12

Fig22: *In vitro* buoyancy studies of optimized formulation

- The *in-vitro* floating behavior of the tablets was studied by placing them in beaker containing 0.1 N HCl (pH 1.2). The gas generating agents immediately evolves carbon dioxide in presence of HCl solution generating sufficient porosity which helped the dosage unit to float. Formulation F1-F3 prepared with carbopol934p started floating after 52 seconds and remains buoyant for 10 hr till they were completely eroded.
- On the other hand formulation F4-F6 prepared with Xanthan gum which shows a floating time of 8hrs and formulation of F7-F9 prepared with HPMC K100M show decrease in floating lag time to 34 seconds and increased floating duration time to >12hrs. This might be due to high viscosity polymer HPMC K100M maintains the integrity of the tablets for longer duration by reducing the effect of erosion thus resulting in increase in floating time. The results are shown in table no.16.Thus it can be concluded that the batch containing HPMC polymers showed good floating lag time and total floating time.

6.7 *In-Vitro* DRUG RELEASE STUDIES:

In-vitro drug release studies were carried out using USP dissolution apparatus type II at 50 rpm. The dissolution medium consisted of 900 ml of pH 1.2 acid buffer (0.1N HCl), maintained at 37 $\pm$ 0.5^{0}C. The drug release at different time intervals was measured using an ultraviolet visible spectrophotometer at 224 nm.

Table no.17: Percentage drug release of formulations

Time (hrs)	Formulations								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	24.87	22.92	20.06	38.34	33.28	27.54	23.46	22.43	17.84
2	36.24	33.82	29.71	52.15	45.38	38.15	36.87	31.11	24.18
4	58.16	55.27	48.07	81.67	64.19	56.77	57.82	53.67	43.67
6	76.08	71.18	69.18	96.44	81.23	79.26	72.09	65.28	61.08
8	87.28	85.33	78.92	96.94	97.61	96.13	83.12	76.59	69.49
10	94.79	91.67	86.13	97.96	97.92	98.21	94.65	88.76	83.54
12	96.53	93.11	88.33	98.1	98.67	98.72	98.74	98.34	90.03

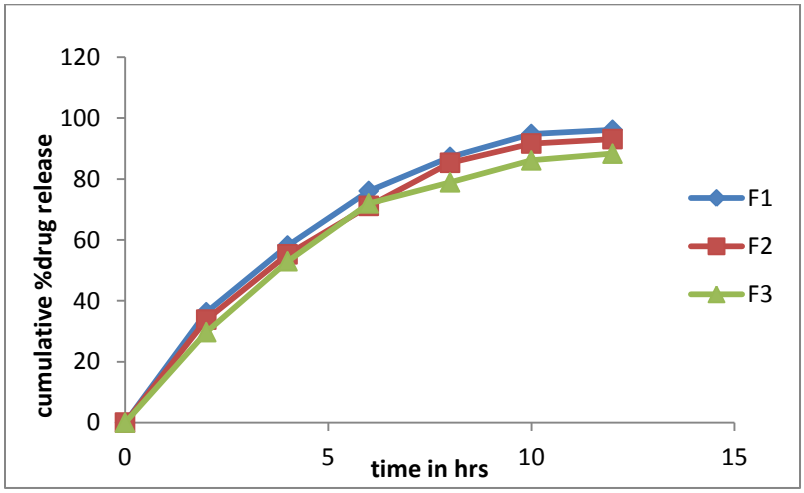


Fig23: *In-vitro* dissolution profile of F1 to F3 formulations.

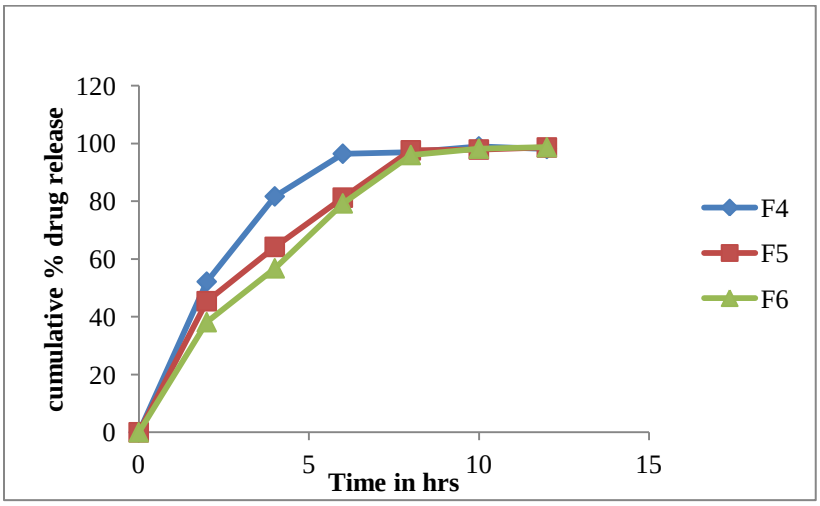


Fig24: *In-vitro* dissolution profile of F4 to F6 formulations.

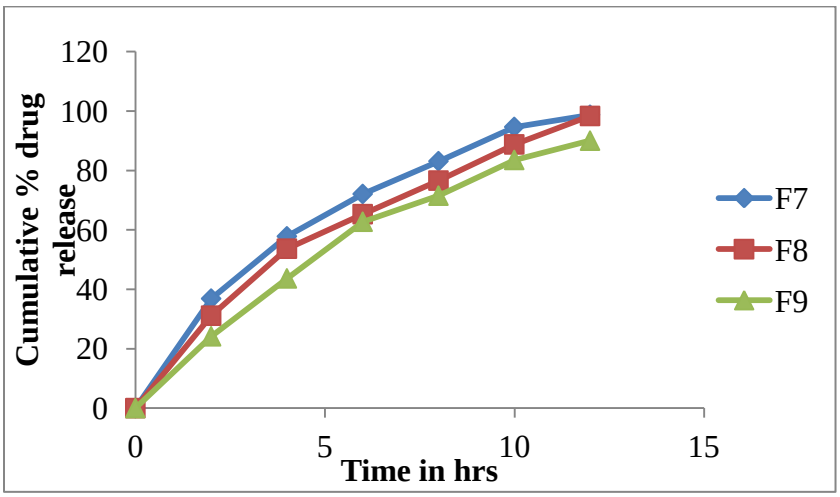


Fig25: *In-vitro* dissolution profile of F7 to F9 formulations.

- *In-vitro* dissolution studies were performed for all the formulations using USP dissolution apparatus II at 50 rpm using 900 ml of 0.1N HCl as dissolution medium. The samples withdrawn and were analyzed by using UV spectrophotometer. The drug release from the formulations F1-F3 prepared with Carbopol 934P was found to be 96.53, 93.11 and 88.33%, formulations F7-F9 prepared with HPMCK100M was found to be 98.74, 98.34, 90.07% showed reasonable drug release, where as formulation F4- F6 prepared with Xanthan gum was found to be 96.94, 97.61, 96.13 at the end of 8 hours. As per the results of dissolution study the formulations F1-F9 the drug release was sustained for 8 to 12hr.
- All the formulations were designed as dosage form for 12 hours. In order to check the 100% dissolution release profile, formulations were subjected to dissolution studies for 12 hours. Among the nine formulations F8 was best and shows 98.34% drug release in the end of 12 hours.
- It is evident from the *in-vitro* dissolution data that increase in HPMC K100M concentration decreases the release rate this might be due to increase in diffusional path length, which the drug molecule may have to travel. . So, formulation F8 was selected as the optimized formulation. The results are shown in table no.17.

6.8 RELEASE KINETICS:

Table No. 18 Model fitting for formulation F-8

Time in hrs.	% release	Log % un-release	Log t	SQRT	Log Cum %CDR
0	0	2	0	0	0
1	22.43	1.91	1	1	1.33
2	31.11	1.83	0.30103	1.414214	1.49
4	53.67	1.67	0.47712	1.73205	1.72
6	65.28	1.54	0.60206	2	1.81
8	76.59	1.38	0.69897	2.23606	1.88
10	88.76	0.77	0.778155	2.44949	1.94
12	98.34	0.29	0.845098	2.64575	1.99

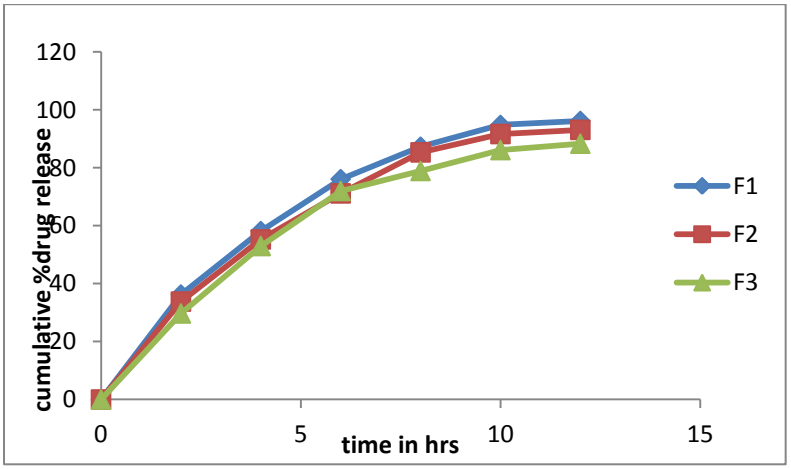


Fig26: Zero order kinetic model of F1 F2 F3

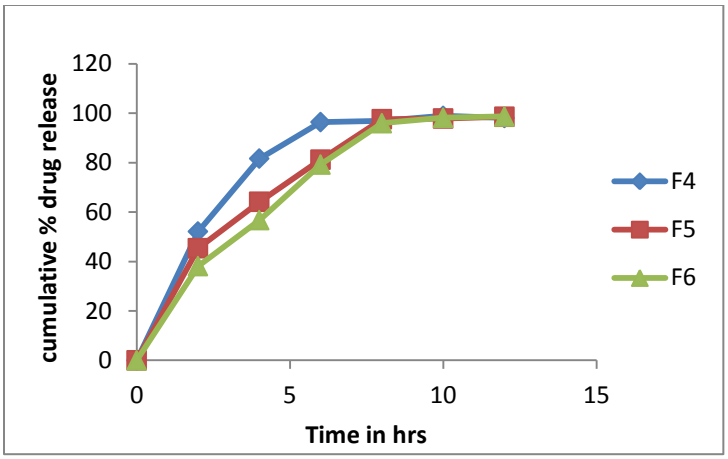


Fig27: Zero order kinetic model of F4 F5 F6

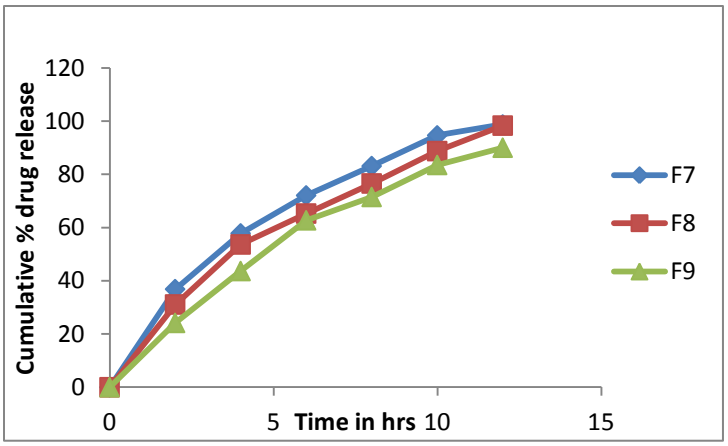


Fig28: Zero order kinetic model of F7 F8 F9

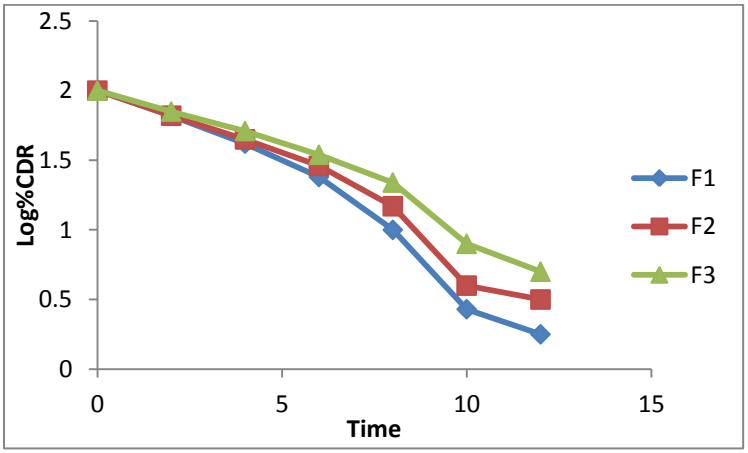


Fig29: First order kinetic model of F1 F2 F3

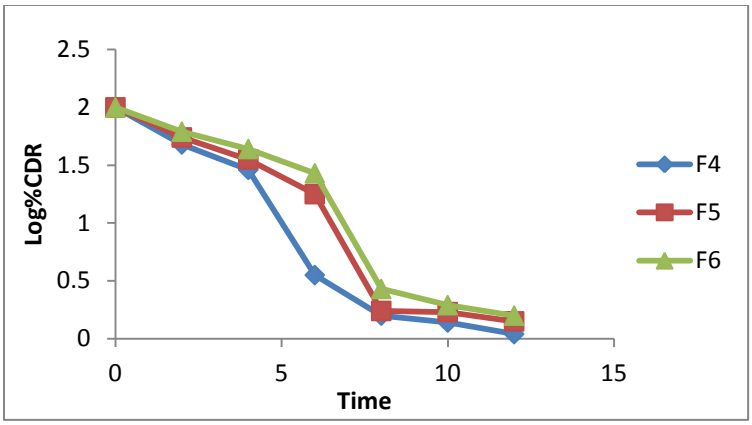


Fig30: First order kinetic model of F4 F5 F6

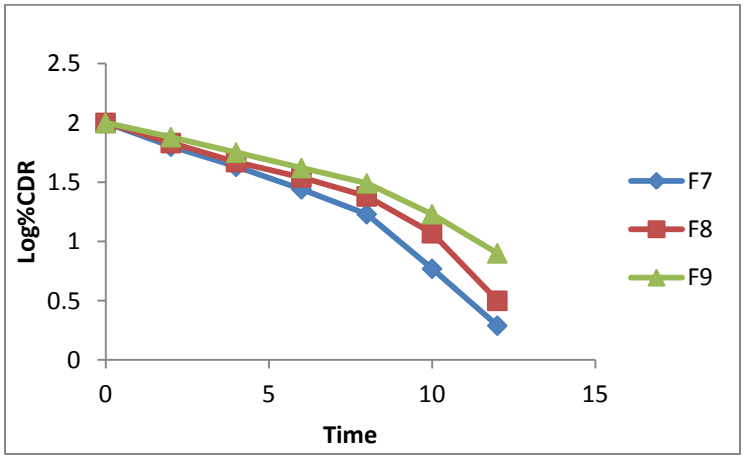


Fig31: First order kinetic model of F7 F8 F9

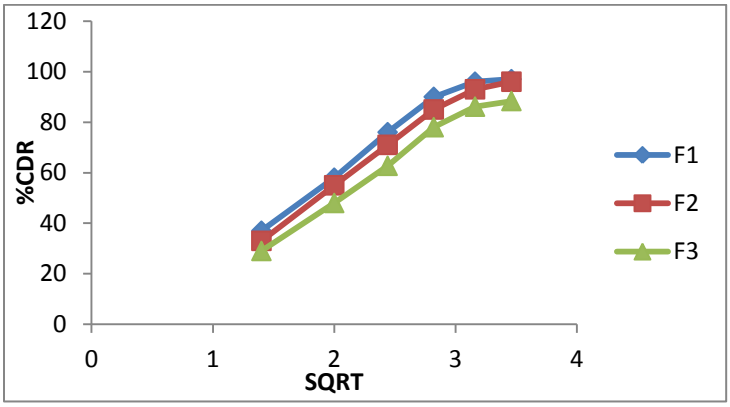


Fig32: Higuchi model of F1, F2, F3

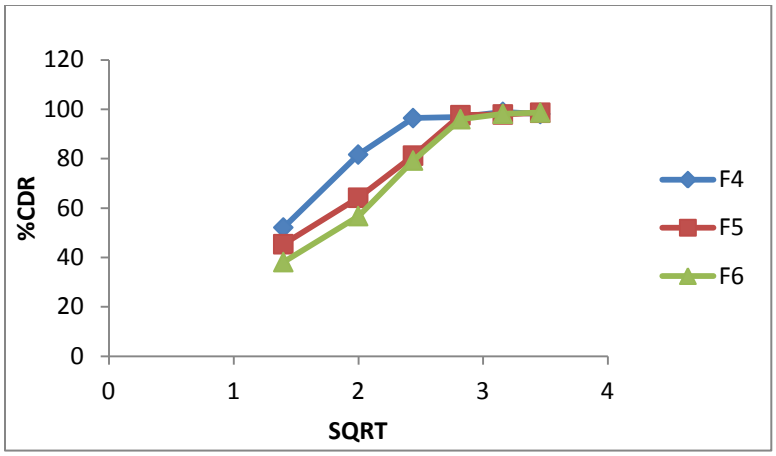


Fig33: Higuchi model of F4, F5, F6

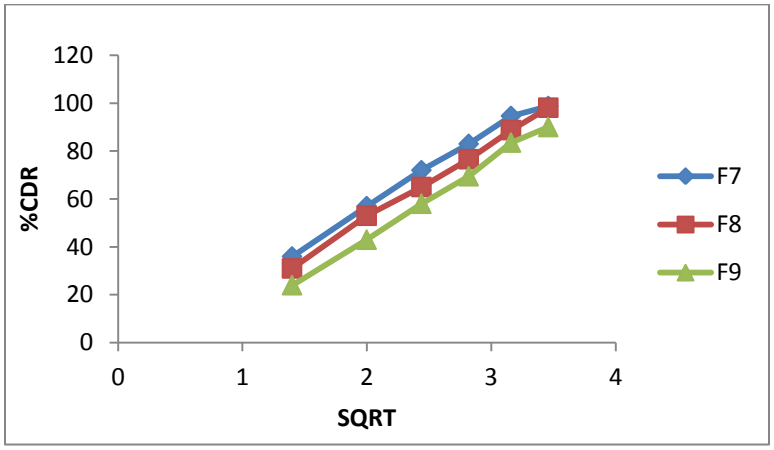


Fig34: Higuchi model of F7, F8, F9

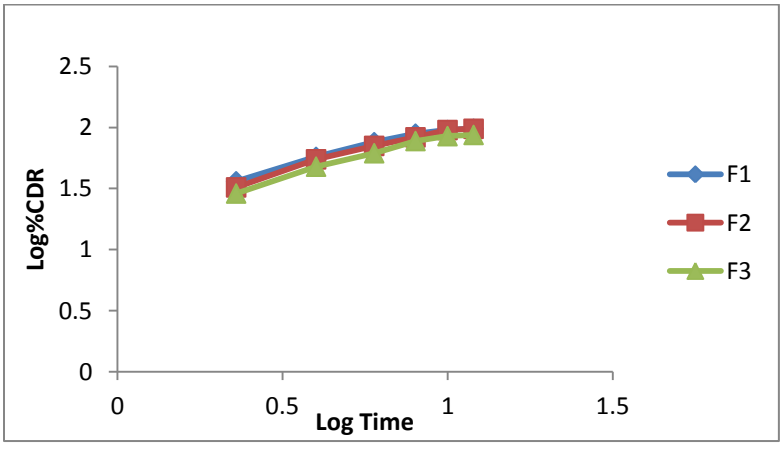


Fig35: Peppas model of F1, F2, F3

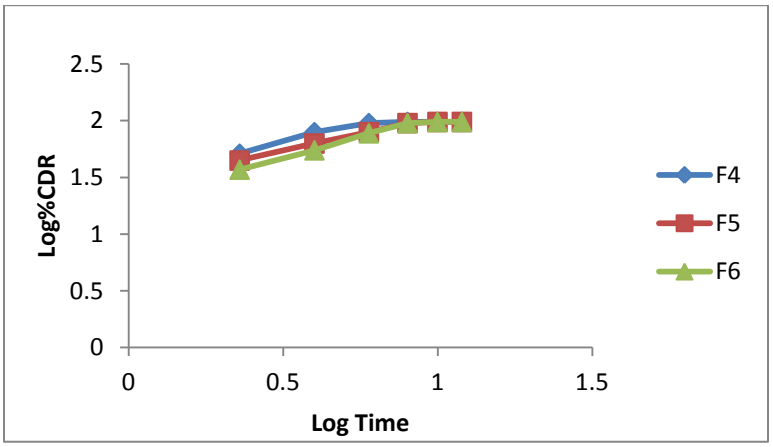


Fig36: Peppas model of F4, F5, F6

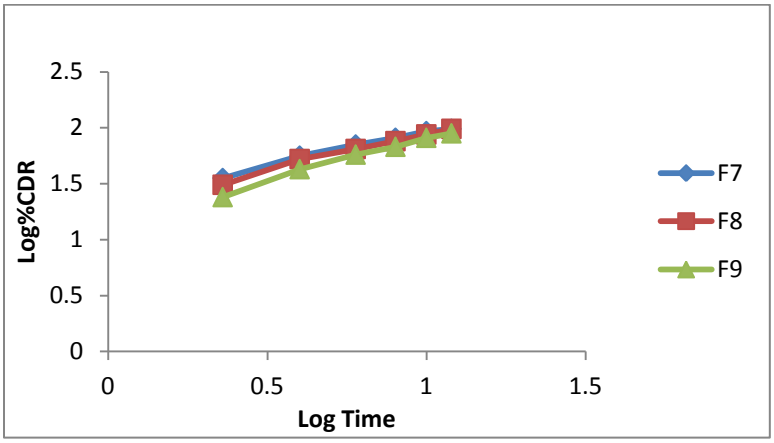


Fig37: Peppas model of F7, F8, F9

Table No. 19 Correlation coefficients of different mathematical models for F-1 to F-9

FORMULATION	ZERO ORDER R^2	FIRST ORDER R^2	HIGUCHI R^2	PEPPAS	
				R^2	n value
F1	0.891	0.938	0.961	0.964	0.612
F2	0.912	0.947	0.984	0.972	0.579
F3	0.934	0.979	0.987	0.987	0.586
F4	0.830	0.872	0.857	0.878	0.457
F5	0.886	0.907	0.893	0.885	0.466
F6	0.898	0.926	0.935	0.959	0.569
F7	0.925	0.947	0.990	0.985	0.669
F8	0.959	0.953	0.998	0.987	0.660
F9	0.974	0.958	0.995	0.982	0.716

- The *in-vitro* drug release data of the floating tablets were evaluated kinetically by zero order kinetics; first order kinetics, Higuchi plot and Peppa's models. The regression coefficient (R^2) value for Zero order, First order, Higuchi's, and Peppa's plots for optimized formulation F8 was found to be 0.959, 0.953, 0.998, 0.987.The optimized formulation F8 follows Higuchi's plot since the regression coefficient is 0.998 also plots were found to be linear, which indicates that the drug release depended on the square root of the time and predominantly controlled by diffusion process.

- The mechanism of drug release is predicted by using Korsmeyer–Peppas equation. The n value of optimized formulation F8 is 0.66 respectively and is between "0.45 to 0.85". This indicates that the drug release depends on swelling, diffusion, and erosion. All formulations follow the non-Fickian/anomalous type of diffusion.

6.9 STABILITY STUDIES:

Table no. 20: Stability studies of optimized formulation F8

Time(days)	**25°C ± 2°C/60% RH ± 5% RH, 30°C ± 2°C/65% RH ± 5% RH, 40°C ± 2°C/75% RH ± 5% RH**			
	Hardness(kg/cm^2)	**Drug content (%)**	**% Drug release**	**Total floating time**
30	5.56	98.45	98.34	>12
60	5.56	98.42	98.27	>12
90	5.48	98.18	98.71	>12

- Stability studies were carried out on selected formulations (F8) as per ICH guidelines. There was not much variation in matrix integrity of the tablets at all the temperature conditions. There was no significant changes in drug content, physical stability, hardness, friability, drug release, floating lag time (Table 20) for the selected formulation F8 after 90 days at 25°C± 2^{0}C / 60% ± 5% RH, 30^{0}C ± 2^{0}C / 65% ±5% RH and 40^{0}C ± 2^0 / 75% ± 5% RH.

6.10 COMPARISON WITH MARKETED PRODUCT:

Table no.21: Comparative studies with optimized formulation

Time(hrs)	Cumulative % drug release	
	F8	Marketed product
1	22.42	27.64
2	31.11	37.18
4	53.67	56.79
6	65.28	74.28
8	76.59	92.08
10	88.76	96.16
12	98.34	96.87

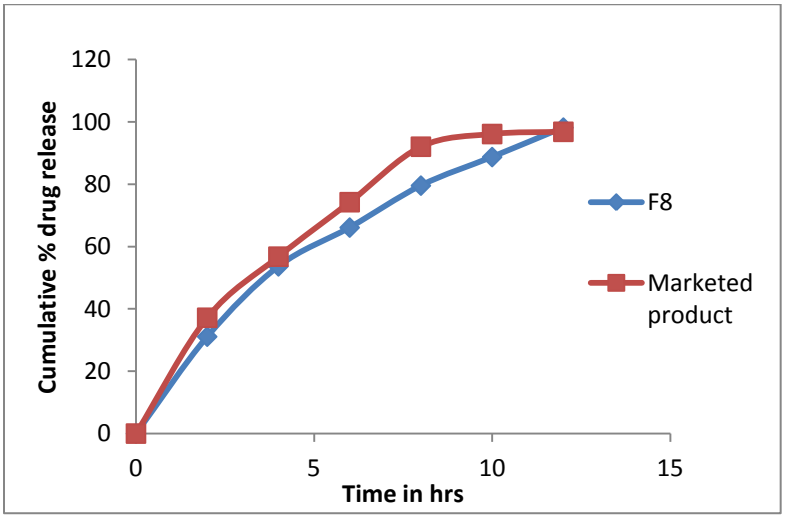


Fig38: Plot of comparative dissolution profile of optimized formulation (F8) and Marketed product

- The marketed product releases 96.16% drug in 10 hrs where as the optimized formulation F8 releases 98.3% of drug in 12 hrs. Thus comparison study of the marketed product of Venlafaxine HCl showed that the optimized formulation F8 has better control over release rate in comparison to the commercial product.

CHAPTER VII

SUMMARY & CONCLUSION

7. SUMMARY AND CONCLUSION

Floating Drug Delivery System are retained in the stomach for a longer time and assist in improving the oral controlled delivery of drugs that have an absorption window in the particular region of the GI tract as well as for controlling the release of the drug having site-specific absorption limitation.

Venlafaxine HCl is a highly effective antidepressant was used as a model drug to develop a controlled release formulation. Venlafaxine HCl exhibits pH dependent solubility. It is more soluble in acidic pH and slightly soluble at neutral or alkaline condition (intestinal environment). Hence an attempt was made to develop gastroretentive delivery system of Venlafaxine HCl which increased the bioavailability of Venlafaxine HCl and also to reduce frequency of administration, thereby improving patient compliance and therapeutic efficacy.

In the present work, 9 different formulations were prepared by direct compression, incorporating polymers like Carbopol934, Xanthan gum and HPMC K100M as swelling polymers, sodium bicarbonate as gas generating agent, MCC as a diluents, talc used as glidant and magnesium stearate used as lubricant.

Characterization of the drug was done by performing the UV spectroscopy and IR spectroscopy. IR spectrum of the pure drug was compared with that of physical mixture of drug with all the excipients used in the study. The results showed that there was no drug-excipient interaction. The UV spectral analysis of the drug solution indicated that λmax value as 224 nm.

All the prepared floating formulations were evaluated for hardness, friability, uniformity of weight, drug content uniformity, drug-polymer interaction, *in-vitro* floating studies, *in vitro* drug release and short term stability studies.

The thickness of the formulations (F1-F9) was in the range of 3.62 ± 0.03 to 3.71 ± 0.05mm and the hardness was in the range of 5.3 ± 0.2 to 6.1 ± 0.3 Kg/ cm^2, indicated good mechanical strength of the tablets. Friability, weight variation and drug content uniformity was found to be within official limits for all the formulations.

The dissolution studies were carried out for 12 hrs. As per the result of dissolution study formulationF1, F2, F7, and F8 showed reasonable release respectively. But F8 showed good floating lag time and total floating time, when compare to other formulations. Based on all these results, formulation F8 was selected as the optimized formulation. F8 was then compared to the marketed product and was found that the optimized formulation F8 has better control over release rate in comparison to the commercial product.

The release kinetics were fitted to different mathematical models like Zero order, First order, Higuchi's and Peppa's plot. The selected formulation F8 follows Higuchi's plot and slope (*n*) value of Peppa's for these formulations were found to be in the range of "0.45 to 0.85". This indicates that the drug release depends on swelling, erosion, and diffusion. Thus follows the non-Fickian/anomalous type of diffusion.

The drug-polymer ratios, viscosity of polymers, were found to influence the drug release and floating properties of the prepared tablets. From the results it can be concluded that as the concentration of the polymer increased floating lag time decreased and the percentage drug release was prolonged. Viscosity of the polymer also showed a directly proportional relationship with swelling characteristics of the tablets.

The optimized formulation (F8) was subjected for stability studies as per ICH guidelines. Formulations subjected for short term stability studies were checked for drug content, hardness, friability and Total floating time for 90 days with an interval of 15 days. The formulations were found to be stable as no significant change was observed in the various evaluated parameters of the formulations.

CHAPTER VIII

REFERENCE

8. REFERENCE

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